Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease–dementia–aphasia syndrome

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Summary

We report six patients with clinically diagnosed and electrophysiologically confirmed motor neurone disease (MND), in whom communication problems were an early and dominant feature. All patients developed a progressive non-fluent aphasia culminating in some cases in complete mutism. In five cases, formal testing revealed deficits in syntactic comprehension. Comprehension and production of verbs were consistently more affected those that of nouns and this effect remained stable upon subsequent testing, despite overall deterioration. The classical signs of MND, including wasting, fasciculations and severe bulbar symptoms, occurred over the following 6–12 months. The behavioural symptoms ranged from mild anosognosia to personality change implicating frontal-lobe dementia. In three cases, post-mortem examination has confirmed the clinical diagnosis of MND–dementia. In addition to the typical involvement of motor and premotor cortex, particularly pronounced pathological changes were observed in the Brodmann areas 44 (Broca’s area) and 45. The finding of a selective impairment of verb/action processing in association with the dementia/aphasia syndrome of MND suggests that the neural substrate underlying verb representation is strongly connected to anterior cortical motor systems.

Keywords: aphasia; frontotemporal dementia; motor neurone disease; verb processing

Abbreviations: BA = Brodmann area; MND = motor neurone disease; TROG = test of the reception of grammar; VOSP = visual object and space perception battery

Introduction

Motor neurone disease (MND) [often referred to as amyotrophic lateral sclerosis (ALS) in northern America and continental Europe] constitutes one major clinical phenotype within the more broadly defined MND group and has traditionally been regarded as predominantly affecting motor function and sparing behaviour, perception, language and other cognitive domains. Charcot, who first delineated the disease in the late 19th century, failed to mention mental symptoms, but a few years later Marie observed ‘childish’ and ‘credulous’ behaviour in some of the patients (quoted in Wechsler and Davison, 1932). This impression was confirmed by a number of early 20th century authors who described cases of MND with prominent cognitive and/or behavioural involvement (Meyer, 1929; Ziegler, 1930; von Braumühl, 1932; Wechsler and Davison, 1932; Teichmann, 1935; Uematsu, 1935). A variant of MND associated with early and prominent dementia was also reported from Japan (Furukawa, 1959; Nagano et al., 1977; Mitsuyama and Takamiya, 1979; Mitsuyama, 1984; Morita et al., 1987). Although it was postulated that the Japanese cases form a separate diagnostic entity (Mitsuyama and Takamiya, 1979), close scrutiny of them has revealed that they share most clinical and pathological features with those reported from Europe and North America (Bak and Hodges, 2000). Further evidence in favour of an association between MND and dementia gradually accumulated over the following decades, such that it is now generally agreed that this cannot simply be a co-occurrence of unrelated conditions (for reviews, see Brion et al., 1980; Hudson, 1981; Bak and Hodges, 1999).

Pathological examination of MND–dementia cases from
Europe, America and Japan show classic changes of MND with neuronal loss in the anterior horn of the spine and bulbar nuclei plus a widespread cortical, mainly frontotemporal, atrophy. Microscopical examination shows evidence of microvacuolation, but no changes suggestive of Alzheimer’s, Pick’s or Lewy body disease (Mitsuyama, 1984; Neary et al., 1990). In recent years growing importance has been attached to the presence of ubiquitin-positive but tau-negative inclusions, occurring in the frontotemporal cortices and granule cells of the dentate fascia as well as in the motor neurones (Okamoto et al., 1991; Wightman et al., 1992). They are, however, not exclusive to MND and were described recently in a purely cortical distribution in three patients clinically presenting as semantic dementia (Rossor et al., 2000).

The majority of cases with MND–dementia show features consistent with frontotemporal dementia characterized by personality change, irritability, apathy, stereotypic behaviour, poor insight and pervasive deficits on frontal-executive tests. Obsession and preoccupation with food seem to be particularly common (van Reeth et al., 1961). In contrast, the visuospatial abilities tend to be relatively well preserved (Neary et al., 1990). In those cases in which a resemblance to other forms of dementia, e.g. Klüver–Bucy syndrome (Dickson et al., 1986) or ‘thalamic dementia’ (Deymeer et al., 1989), have been postulated, the clinical details provided reveal characteristic features of frontal dementia while the pathological evaluation refers to atrophy of frontal lobes. Progression in all cases tends to be rapid, leading to death within 2–3 years.

In comparison with behaviour and frontal-executive functions, little attention has been paid to the language disturbance associated with the MND–dementia syndrome. This is surprising since most descriptions contain some reference to language involvement. The most frequently mentioned change is reduced verbal output, often leading to complete mutism within a few months. Another commonly reported symptom is the use of stereotypic expressions, perseverations and echolalia (Mitsuyama, 1984). Several reports mention impaired naming (De Morsier, 1967) and comprehension (Mitsuyama and Takamiya, 1979; Neary et al., 1990), although the latter tends to be attributed to deficits in abstract reasoning or to general dementia rather than to a specific linguistic deficit (Neary et al., 1990; Peavy et al., 1992). More explicit aphasic symptoms, e.g. ‘semantic paraphasias’, were also reported (Neary et al., 1990). A comprehensive overview of language and speech abnormalities found in patients with MND is provided by Strong (Strong et al., 1996).

In the first detailed report of aphasia with MND, Caselli and colleagues presented seven patients in whom progressive non-fluent aphasia was the presenting and dominant feature (Caselli et al., 1993). In addition to the prominent bulbar symptoms, all patients showed clear evidence of aphasia, both in spoken and written language. Comprehension was described as ‘significantly impaired’, without further clarification. Behavioural abnormalities were much less pronounced than in other cases of MND–dementia syndrome. Doran et al. (1995) also reported five patients with rapidly progressive MND and aphasia; three showed significant deficits in syntactic comprehension. Unfortunately, the neuropathological examination was not obtained in these three cases. In the other two cases, who did not undergo detailed neuropsychological assessment, the pathological changes were not characteristic for MND. One patient had neurofibrillary tangles and neuritic plaques with the immunohistological profile typical of Alzheimer’s disease, but in an atypical distribution in that they involved the perisylvian cortex and virtually spared the medial temporal lobe structures. In the other case, significant neuronal loss and non-specific cortical spongiosia were prominent with numerous cortical Lewy bodies. These observations raise the question of whether MND–aphasia can pathologically be considered a subtype of MND–dementia or as a separate, possibly heterogenous syndrome. However, the fragmentary character of the data currently available leaves this question unanswered. A further single case report was reported recently by Tsuchiya and colleagues which mentioned production and comprehension deficits, but without any linguistic characterization or formal language testing (Tsuchiya et al., 2000). Also, non-demented MND patients can develop language-related deficits. In a study of 20 unselected patients, Rakowicz and Hodges (1998) found three patients with impaired language in the absence of a generalized dementia, suggesting that language dysfunction might be more common than originally assumed. The exact nature of the linguistic deficits in MND remains elusive. In particular, to date no study has investigated a possible dissociation between the processing of different word classes in patients with MND.

Selective deficits affecting specific word classes have been well established in the aphasiological literature since the 18th century (for verbs, Vico, 1744; for nouns, Linnaeus, 1745). In recent times, a number of single case and group studies have confirmed the presence of noun–verb dissociations in language production and comprehension (McCarthy and Warrington, 1985; Zingeser and Berndt, 1990; Berndt et al., 1997). In stroke patients, on whom the majority of the studies have been conducted, selective verb impairment tends to be associated clinically with agrammatism (for exceptions, see Caramazza and Hillis, 1991; Kremin and Basso, 1993) and anatomically with an occlusion of the anterior branch of the medial cerebral artery. In contrast, noun impairment has been associated anatomically with occlusion of the posterior branch of the medial cerebral artery and clinically with the presence of anomia (Miceli et al., 1984; Miceli and Caramazza, 1988). Similar patterns have been observed in English and Italian, as well as in non-Indo-European languages like Chinese (Bates et al., 1991). Recent reports of patients with progressive supranuclear palsy (Daniele et al., 1994) and frontotemporal dementia (Cappa et al., 1998) suggest that verb impairment may be linked to a dysfunction in frontal and frontostriatal circuits. We postulated that MND-associated
dementia might be particularly liable to affect processing of verbs to a greater degree than that of nouns. To date, no study has investigated this claim. The aims of this study were to investigate the nature of the aphasia seen in a group of patients with the MND–dementia syndrome, to test specifically the hypothesis that verb production and/or comprehension are selectively vulnerable and to explore the anatomical basis of this dissociation (if present) by neuropathological evaluation.

### Methods

**Patients**

Between 1996 and 1999, six cases of MND with dementia and/or aphasia were examined (demographic and clinical features are summarized in Table 1). Case 5 was investigated initially at the Aberdeen Royal Infirmary, and all other patients at Addenbrooke’s Hospital, Cambridge. Apart from Case 4, all have been followed up and assessed at home/nursing home after their discharge from hospital. A structural (CT and/or MRI) brain scan, evidence for motor denervation on EMG and nerve conduction studies were conducted for all patients. Four patients (Cases 1, 2, 3 and 6) also had a functional (HMPAO-SPECT) brain scan. In these four patients the relatives agreed to brain tissue donation (including the spinal cord in Cases 1 and 6) and a detailed gross and microscopic pathological examination was performed.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age of onset (years)</th>
<th>Initial presentation</th>
<th>Disease duration</th>
<th>CT/MRI</th>
<th>SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>49</td>
<td>Reduced speech, hoarding, gluttony</td>
<td>Death within 3 years</td>
<td>Normal</td>
<td>Frontal hypoperfusion</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>67</td>
<td>Reduced speech</td>
<td>Death within 2 years</td>
<td>Left temporal atrophy</td>
<td>Parietal hypoperfusion</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>49</td>
<td>Dysarthria, mental slowing</td>
<td>Death within 2 years</td>
<td>Frontal atrophy</td>
<td>Frontal hypoperfusion</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>64</td>
<td>Dysarthria, anemia</td>
<td>Death within 2 years</td>
<td>Left temporal atrophy</td>
<td>Not performed</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>70</td>
<td>Personality change, slurred speech</td>
<td>Death within 2 years</td>
<td>Generalised atrophy</td>
<td>Not performed</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>52</td>
<td>Apathy, delusions hallucinations</td>
<td>Death within 2 years</td>
<td>Frontotemporal atrophy</td>
<td>Frontotemporal hypoperfusion</td>
</tr>
</tbody>
</table>

### Tests

Sentence comprehension was assessed with the help of the test of the reception of grammar (TROG), developed by Bishop (1989). It consists of 80 different sets of four coloured drawings. The subject is given a word or a sentence and asked to point to the appropriate picture. The entire test is subdivided into 20 thematic blocks. Each consists of four sets of pictures and examines different syntactic structures of increasing degree of difficulty, from single nouns, verbs and adjectives and two word combinations to complex relationships, e.g. reversible passive, embedded sentences and negation (see Appendix I). The result of the test can be expressed as the total number of items answered correctly (maximum 80) or as the number of blocks passed (maximum 20). The pattern of errors across the blocks can be analysed separately. In this way the TROG gives quantitative and qualitative information about the nature of the syntactic deficit. In order to focus on the syntactic properties of the examined structures, the vocabulary utilized and the visual form of the pictures is kept as simple as possible. In addition, the sentence length is kept constant for tasks of different syntactic complexity, minimizing the effects of a possible attentional and short-term memory impairment. These two aspects are of particular importance when investigating patients with neurodegenerative diseases affecting several cognitive domains (Croot et al., 1999).

To assess verb and noun processing, a test of naming and comprehension was adapted from that of Berndt (Berndt et al., 1996). In the naming part, the subject is shown 40 black and white drawings and asked to name each one with as few words as possible. In the comprehension subtest, the subject is given 50 pairs of drawings depicting either two objects or two actions and is asked to point to the one that matches a word read by the examiner. Since both tests utilize the same drawings, they are administered in two separate sessions: first naming, then comprehension. Unfortunately, several patients were already mute at the time of their initial assessment and were not able to complete the naming part of the test.

The profound nature of aphasia in our patients made testing of other cognitive functions extremely difficult. To assess the visuospatial abilities, we were able to obtain drawings (e.g. a copy of the Rey–Osterrieth figure or other meaningful or geometrical structures) in some of the patients (Cases 1, 2, 3 and 6). In addition, Cases 1, 2 and 3 were administered subtests of the visual object and space perception battery (VOSP) (Warrington and James, 1991). In the subtest ‘incomplete letters’, patients are asked to name visually degraded letters, in ‘object decision’ to choose one of four silhouette drawings corresponding to a real object, in ‘dot counting’ to count the number of dots (between six and 10) presented in a picture, and finally in ‘cube analysis’ to count the number of cubes (between three and 10, some of them hidden, requiring manipulation of the mental image) in a drawing.
Healthy controls
Although normative data has been collected already for the noun and verb naming and comprehension tests (Berndt et al., 1997), taking into consideration the different usage of certain words in American and British English we decided to administer it to 20 English, healthy controls (mean age 68.3 years, SD = 5.64, range 54–78; mean Mini-Mental State Examination score 29.2, SD = 0.81, range 28–30) from a similar geographic and social background, enrolled via the MRC–Cognition and Brain Sciences Unit Subject Panel.

Alzheimer’s disease controls
Normal controls performed near ceiling on all three tests (TROG, noun and verb naming and noun and verb comprehension). A qualitative analysis of the linguistic deficits that might be characteristic for MND–aphasia required, therefore, an inclusion of a second control group, ideally with another neurodegenerative condition affecting cognition in general and language in particular, but with a clinical picture and pathological changes different to those described in MND–dementia. Alzheimer’s disease patients show semantic (Hodges and Patterson, 1995) and mild syntactic (Croft et al., 1999) impairments, but the general pattern of their deficits, dominated by a prominent amnesia, and the pathological changes involving medial temporal and posterior association cortices, are clearly different from MND–dementia. Although this approach clearly has its limitations, since the patients in the Alzheimer’s disease group have their own language problems, it does allow a comparison between different patterns of impairment. The Alzheimer’s disease group consisted of 20 patients with mild to moderate disease (mean age 70.2 years, SD = 4.9, range 64–78; mean Mini-Mental State Examination score 25.2, SD = 4.5, range 10–30).

All patients, relatives and controls gave informed consent to participate in the study, which was approved by the Cambridge Local Research Ethics Committee.

Statistical analysis
All statistical analysis was performed using the SPSS package (SPSS Inc., Chicago, Ill., USA). For comparison of results between the three groups (MND patients, Alzheimer’s disease patients and controls) the Mann–Whitney U test was applied. The comparison of results for nouns and verbs within each group was performed using the Wilcoxon matched pairs test.

Pathological and histopathological techniques
Whole brain and spinal cord organs from four Cases (1, 2, 3 and 6) were collected by the Cambridge MRC Brain Bank. Ethical approval for the retention of brain and spinal tissue was obtained for the study, and informed consent was given by the families of the patients. The left cerebral hemisphere, left half brainstem, right cerebellar hemisphere and remnant of the left cerebellar hemisphere from all four necropsy cases (Cases 1, 2, 3 and 6) were fixed in formalin. The spinal cords of two cases (1 and 6) were also fixed in formalin. The right cerebral hemisphere, right half brainstem and a section of the left cerebellar hemisphere, including the dentate nucleus from all four necropsy Cases 1, 2, 3 and 6, were frozen and stored.

The formalin-fixed half brains were examined and the hemispheres were coronally sectioned at 0.5-cm intervals. The cerebellar hemispheres were sectioned in the rostrocaudal plane at right angles to the folia, and the half brainstems were sectioned at 0.5-cm intervals. Sections were sampled to allow both the CERAD protocol and Braak staging with additional areas 1 (Mirra et al., 1991). This included Brodmann areas (BA) 3/1/2, 4, 6, 10, 17, 21/22, 37, 38, 39, 40, 44, 45, the cingulate gyrus, entorhinal cortex, hippocampal formation, basal ganglia, midbrain at two levels, pons and medulla at several levels. The cerebellar vermis and right hemisphere, including the dentate nucleus, were also sampled. Three consecutive 0.5-cm-thick sections of the mid-cervical, mid-thoracic and mid-lumbar cord were taken from the two cases with available spinal cord tissue. All sections were stained with haematoxylin and eosin. Immunohistochemistry was undertaken using antisera to ubiquitin, tau and GFAP (glial fibrillary acidic protein) on selected cortical blocks and spinal cord sections.

Case histories
Case 1
A 51-year-old right-handed man presented with a 2-year history of difficulty in communicating and behavioural changes. His spontaneous speech became reduced (but not dysarthric) and he frequently missed out portions of sentences, communicating first in a ‘telegraphic way’, then mainly through pointing, as he became progressively mute. He started to hoard bric-a-brac and rubbish, filling three caravans and four sheds, and became obsessed with food, overeating and hoarding large quantities of baked beans and pork pies. He lost interest in his social life, hobbies and sex. His wife described his behaviour as aggressive and irritable, but at the same time also ‘childish and clinging’. There was a family history of vascular disease in his parents and Down’s syndrome in a sister, but no personal medical history apart from a mild depressive episode 20 years before, which resolved without treatment. Neurological examination was initially normal, apart from positive frontal release signs and difficulty in motor sequencing. Verbal output was severely reduced and he produced occasional semantic paraphasias on naming tasks. Within a few weeks he became entirely mute and his written speech was incomprehensible (as can be seen from the written description of the Boston Cookie Theft picture in Fig. 1). In contrast, his ability to draw and copy was remarkably well preserved (see Fig. 2). Routine blood
Impaired verb processing in MND–dementia

Fig. 1 The Boston Cookie Theft picture and written descriptions of it by the Case 1 and Case 2 patients.

Case 1

Case 2

Fig. 2 Copy of the Rey–Osterrieth figure by Case 1.

tests were normal, as was a cerebral MRI, but a HMPAO-SPECT showed bifrontal hypoperfusion. A clinical diagnosis of frontotemporal dementia was made. The patient continued to deteriorate displaying disinhibition, utilization behaviour and repetitive phenomena including echopraxia. Six months after his initial presentation he developed wasting and fasciculations in all limbs, but without any significant weakness. His reflexes remained brisk. The EMG was consistent with early anterior horn cell disease and the diagnosis was revised to MND–dementia–aphasia complex. The rapid emergence of bulbar symptoms led to difficulty in swallowing and subsequent weight loss. Due to violent and uncontrollable behaviour he was admitted to the psychiatric ward and died several weeks later, 3 years after the onset of symptoms. A post-mortem examination was performed and will be discussed together with the results of the other patients.

Case 2

A 67-year-old right-handed man presented with a 1 year history of communication difficulties and reduced verbal output, but apparently preserved non-verbal cognitive skills. No relevant family history was reported. By the time of his hospital admission 2 months later the patient was virtually mute (although he was still able to write) and had developed difficulty in swallowing. Neurological examination revealed wasting and gross fasciculations in the tongue and all limbs in the presence of brisk reflexes. Frontal release signs were absent. The diagnosis of MND was confirmed neurophysiologically. On a written naming test he produced multiple semantic paraphasias (e.g. ‘hatchet’ for ‘axe’, ‘leopard’ for ‘tiger’ or ‘hippo’ for ‘rhinoceros’) and his
written description of the Boston Cookie Theft picture consisted of a few unconnected two to three word phrases (Fig. 1). Although the patient was cooperative, further testing was limited by the pronounced comprehension deficit. The patient continued to deteriorate and was transferred to a nursing home. He died 18 months after initial presentation. A post-mortem examination was performed and will be discussed together with results of the other patients.

Case 3
A 50-year-old right-handed man presented with a 6-month history of slurred speech and general psychomotor slowing. There was no relevant family history and his own history consisted only of occasional attacks of migraine and lower back pain. In the following months this previously placid man became restless, aggressive, impulsive and disinhibited. He developed paranoid ideas, compulsive checking and overeating. With time his behaviour changed more to a ‘child-like’ disinhibition with lack of concern, but occasional outbursts of violence remained a problem. The emergence of widespread fasciculations, weakness, wasting and brisk reflexes in all limbs with extensor plantar response bilaterally led to the diagnosis of MND, further strengthened by evidence of denervation in the lower limbs upon EMG. Laboratory examinations including CSF, EEG and CT were normal, but an MRI showed a mild degree of frontal atrophy and HMPAO-SPECT identified frontal hypoperfusion. Due to extreme distractability, he was able to complete few formal neuropsychological tests, but his drawings showed a relative preservation of constructional skills. Within 6 months his speech output was restricted to a few odd words. He then deteriorated rapidly and was unable to communicate either through words or gestures and showed no understanding of simple instructions. Progressive dysphagia lead to choking, weight loss and recurrent chest infections. He died of pneumonia 22 months after developing the first symptoms. A post-mortem examination was performed and will be discussed later.

Case 4
A 64-year-old right-handed former university lecturer presented with a 6-month history of slurred speech, later accompanied by anomia and dysphagia. There was no significant family history and his own medical history consisted only of a transurethral resection 4 years before. At the time of investigation his verbal output was severely reduced. He tried to communicate through writing, albeit in a very limited way. His performance on tests of language, including naming and single word comprehension, calculation and frontal-executive function (Weigl Sorting Test: perseverated after one category), was severely impaired. In contrast, his scores on VOSP subtests ‘fragmented letters’ and ‘dot counting’ were within the normal range. The testing was made additionally difficult by only limited cooperation. On neurological examination there were fasciculations of the tongue and all four limbs, accompanied by brisk reflexes and extensor plantarflexes. EMG showed widespread active and chronic partial denervation in all four limbs. All routine laboratory tests were normal. Cranial MRI showed left temporal atrophy and spinal MRI was normal. He continued to deteriorate rapidly, with his verbal output confined to a few incomprehensible sounds. Due to increasing muscle weakness he became wheelchair-bound and died several weeks later, <2 years after the onset of initial symptoms. A post-mortem was not performed.

Case 5
A 70-year-old right-handed former midwife presented with a 1-year history of progressive slurring of speech, followed by difficulty in swallowing and forgetfulness. At about the same time her two sisters noted a dramatic personality change: the formerly very orderly and rather withdrawn lady started shoplifting, developed inappropriate, overfamiliar behaviour, particularly towards children, and became extremely rigid in her everyday routines, reacting aggressively to any alterations from her intended plans. This was followed by loss of all interests and hobbies, self-neglect and suspiciousness. The past medical history included rheumatoid arthritis, diagnosed several years previously, and an attack of angina in the preceding year. Apart from one case of multiple sclerosis in a cousin, there is no family history of neurological or psychiatric disease. Initial medical investigations did not show any abnormalities and the patient was prescribed sertraline for presumed depression. While this reduced her anxiety level, the altered pattern of behaviour persisted. As her gait became unstable with several falls, a trial of Sinemet was begun, but she did not improve. The drug was discontinued due to dizziness. She continued to deteriorate and was referred to the neurology department for further assessment. Examination revealed tongue wasting and fasciculation. Muscle wasting, weakness and brisk reflexes were also observed in all four limbs, most pronounced in the hands. Eye movements were delayed in initiation, but normal in speed and range. A CT scan showed generalised cortical atrophy with slight ventricular dilatation. CSF was normal, as were other laboratory tests. Since the patient, previously living alone, was not able to care for herself, she had to move to a nursing home. Bedside cognitive testing revealed widespread deficits with very patchy orientation, markedly reduced verbal fluency, moderate anomia and a severely reduced ability to register and recall new information. Recognition of designs and simple drawings were less impaired. She deteriorated rapidly, lost weight and died ~2 years after the occurrence of the first symptoms and 8 months after diagnosis. A post-mortem was not performed.

Case 6
A previously healthy 53-year-old woman (apart from the history of a head injury with short loss of consciousness in
Fig. 3 Lateral views of formalin-fixed left hemispheres with intact leptomeninges (Cases 1, 3 and 6) and after their removal (Case 2), showing mild to moderate atrophy of the temporal pole (Case 1), moderate atrophy of caudal frontal and rostral parietal lobes (Case 2), moderate atrophy of the frontal lobe including the precentral (motor) cortex, and mild atrophy of the temporal pole (Case 3) and moderate atrophy of the rostral and precentral gyrae of the frontal lobe (Case 6).
a car accident in 1966) presented with a 1-year history of progressive psychiatric symptoms, including apathy, withdrawal, poor concentration and memory as well as hallucinations and delusions involving a phantom lodger, carrying the name of her former boyfriend from teenage years. The family history included senile dementia in her mother, lasting 8 years prior to her death at the age of 91 years. Her father, who died aged 72 years, had impaired
memory for the last few years of his life. One brother and five sisters (all of them older than the patient) were fit and healthy. Apart from positive frontal release signs (glabellar tap, pout, palmomental and grasp reflexes), the neurological examination was normal. Routine blood investigations, CSF and EEG were all normal. CT and MRI scans showed mild, bilateral, mostly frontal and perisylvian atrophy. The SPECT scan demonstrated marked hypoperfusion in frontal, temporal and anterior parietal regions on both sides, as well as reduced perfusion to the left basal ganglia. A clinical diagnosis of frontotemporal dementia was made.

Within 6 months the patient developed mild dysarthria and fasciculations, initially in the tongue and shoulder girdle, later involving the extremities. The EMG confirmed the presence of denervation, supporting the diagnosis of MND. Her speech was initially fluent, but the verbal output decreased dramatically with the progression of dysarthria. The patient showed a tendency to perseverate with pronounced echolalia and, to a lesser degree, echopraxia. Her naming was quick, albeit often inaccurate, but she had great difficulties with any tasks involving decision making and multiple choice alternatives. She had only very limited insight into her disease. Her mood was generally cheerful, with only short occasional outbursts of tears provoked by emotionally challenging situations. Over the next 6 months her speech deteriorated further, fasciculations became more pronounced and there was clear wasting, particularly in the tongue and upper limbs. The reflexes were symmetrically brisk, with bilaterally upgoing plantars. Her husband observed difficulty in swallowing and occasional choking on solid food. She became unable to control micturition and later developed double incontinence. Initially fully mobile, the patient began to experience difficulties negotiating steps and walking long distances. In her last weeks she became fully apathetic, refused food and rapidly lost weight. She died of pneumonia.

A post-mortem examination was performed and will be discussed later.

Results

Summary of clinical features and investigations

All six patients initially presented with difficulty communicating and/or behavioural changes (see Table 1), preceding the development of motor symptoms by several months. Language change was characterized by progressive reduction in spontaneous verbal output, followed by dysarthria and, later, by mutism. It is, however, important to note that, at least in Case 1, the poverty of speech occurred before the emergence of dysarthria and hence cannot be attributed to bulbar dysfunction alone. Cases 1 and 2 were still able to write for several weeks after the loss of their spoken language and their written language revealed numerous semantic paraphasias and syntactic violations, although their handwriting was neat and legible (Fig. 1). Visuospatial skills, tested through copying of drawings (Fig. 2) and VOSP subtests, were relatively well preserved. In addition to the language impairment, Cases 1, 3, 5 and 6 also showed a marked change in personality with features of frontal lobe dysfunction, including disinhibition, irritability, aggressivity, inappropriate behaviour and rigid observance of daily routines. In contrast, the two remaining patients (Cases 2 and 4) did not develop unequivocal features of frontal dysfunction. None of the patients had any significant family history.

Since motor symptoms were not always present on first examination, the initial diagnosis included frontotemporal dementia (Cases 1 and 6) and primary progressive aphasia (Case 2). In all patients, the motor symptoms developed over the following 6–12 months and comprised weakness, wasting, fasciculations and pronounced bulbar involvement with dysphagia and dysarthria. In the later stages, all patients met the El Escorial criteria for probable MND (Brooks, 1994). EMG was performed in all six patients and showed a pattern of denervation with no signs of significant sensory involvement or motor conduction block. These EMG results do not differ from those obtained in ‘classical’ MND patients (who do not show any signs of cognitive and linguistic involvement).

The structural neuroimaging (Table 1) showed, apart from either Case 1 whose initial scan was normal, frontal (Case 3), temporal (Cases 2 and 4), frontotemporal (Case 6) or generalized (Case 5) cortical atrophy. The changes were bilateral, but in Cases 2 and 4 they were more pronounced on the left side. The changes on the SPECT scan were more variable, including frontal (Cases 1 and 3), frontotemporal (Case 6) and parietal (Case 2) hypoperfusion.

Due to pronounced restlessness, the insertion of percutaneous endoscopic gastrostomy (PEG), often used in other diseases affecting bulbar function to guarantee continuous enteral nutrition, was not a viable option. In the terminal stages of disease the patients became cachectic and ultimately succumbed to pneumonia. The overall rate of progression was very rapid, with death occurring 18–36 months after initial presentation.

Neuropathology

Macroscopic examination

All four brains showed mild to moderate frontal lobe atrophy, and moderate atrophy of the left temporal pole (Fig. 3). The three spinal cord specimens showed atrophy and grey discolouration of ventral nerve roots (Fig. 4).

Spinal cord

Histology of the spinal cord of Case 1 showed marked loss of neurones in the cervical and thoracic ventral horns (Fig. 4), and mild changes in the lumbar ventral horns. There was mild pallor of the lateral corticospinal tracts. Ubiquitin-positive skein-like inclusions were present in residual
neurones of the spinal cord. Atrophy of the ventral roots was confirmed. Segments of the upper cervical spinal cord attached to the brainstem were available for examination in Case 2 and also showed ventral horn cell loss. Case 6 showed loss of the medial groups of neurones of the ventral horns in the cervical, thoracic and lumbar segments. Chromatolytic neurones and Bunina bodies were identified. Atrophy of the ventral roots was also confirmed.

**Brainstem**
The hypoglossal nucleus of all four cases (1, 2, 3 and 6) examined histologically showed severe loss of neurones and gliosis. The substantia nigra and locus caeruleus showed moderate loss of pigment cells in Case 1, and mild loss in Cases 2 and 3. No classical Lewy bodies were identified.

**Medial temporal lobe structures**
Case 1 showed a few round and scanty skein-like ubiquitin-positive inclusions in the dentate gyrus of the hippocampus. Tau immunohistochemistry revealed no significant tangle pathology. Case 2 showed numerous dense round ubiquitin-positive tau-negative inclusions in the small neurones of the dentate fascia of the hippocampus (Fig. 5). The brain showed very minor Alzheimer pathology, equivalent to Braak stage 2. Case 3 showed no round or skein-like ubiquitin-positive inclusions in the hippocampus, but numerous tau-positive tangles were present in the transentorhinal cortex. The hippocampus was spared.

**Cerebral hemispheres**
Case 1 showed nerve cell loss with microvacuolation and mild superficial gliosis in frontal and rostral temporal lobe BA 6, 10 and 44/45, involving particularly laminae II and III. Microvacuolation was not pronounced in the motor strip BA 4, but Betz cells were completely absent. The superficial spongiosis also involved the parietal lobe BA 6. Case 2 showed neuronal loss, superficial spongiosis and mild gliosis in the frontal lobe, especially in BA 44/45. Case 3 showed superficial spongiosis in BA 6, 10, 38 and 44/45 without gliosis. Isolated skein-like inclusions but no Lewy-like inclusions were also noted, along with non-specific granular ubiquitinated neuropil and cortical white matter deposits. Also, Case 6 showed neuronal loss and superficial spongiosis in BA 44/45. Figure 6 shows the pathological changes in BA 44 and 45 in Cases 1, 2 and 3 for comparison.

**Summary**
The changes in the spinal cord and brainstem nuclei were entirely consistent with MND. Unlike the two cases described by Doran et al. (1995), there were no pathological changes.
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Fig. 6 BA 44 of Cases 2 and 3 (upper panels) and BA 45 of Cases 1 and 3 (lower panels), showing microvacuolation using haematoxylin and eosin staining.
reminiscent of Alzheimer’s disease and no cortical Lewy bodies. The brunt of the cortical changes fell on the frontal lobe and rostral temporal lobe with microvacuolation of cortical laminae II and III and mild gliosis. Of note was the consistent involvement of BA 44/45 (Broca’s area). Typical MND-associated inclusions were present in the dentate gyrus of the hippocampal formation in two cases. Two showed tau-positive tangles. There was no evidence of the spongiform change that is characteristic of Creutzfeldt–Jakob disease. The loss of neurones from the cerebrum, brainstem nuclei and ventral horn cells contrasted with the relative lack of white matter involvement, which had been acknowledged before in frontotemporal dementia with MND (Mann, 1998), but contrasted with case reports from Japan (Mitsuyama, 1993; Tsuchiya et al., 2000) in which the pyramidal tracts showed marked bilateral degeneration, and with three American cases (Caselli et al., 1993) with mild pyramidal tract degeneration. The cases presented here differ from those of semantic dementia with ubiquitin-positive inclusions, which did not show changes characteristic of MND (Rossor et al., 2000).

**Neuropsychological findings**

**Syntactic comprehension**

The TROG was performed on all patients, except Case 4. Cases 1, 2, 3 and 6 were followed-up ~6 months after initial assessment, but Case 3 was too impaired for further testing. The results are presented in Table 2. All five patients showed a massive impairment of sentence comprehension. The best result obtained by an MND patient (86% correct) was clearly below the worst result of the control group (91%), so that there was no overlap between both groups. The difference between the groups was significant (Mann–Whitney U test, \( P < 0.0001 \)). There was also a significant difference between MND and Alzheimer’s disease patients (Mann–Whitney U test, \( P < 0.0001 \)). Only one Alzheimer’s disease patient had an impairment comparable to that of MND patients (74% correct), but even his performance is better than the mean score of the MND group.

To analyse further the pattern of performance of the TROG, we plotted the percentage of errors made by each group across the 20 blocks of the test (Fig. 7). The proportion of errors increased across the blocks in all three groups, reflecting the growing syntactic complexity of the sentences (see Appendix I). In normal controls, more than half of all errors were made in block T (embedded sentences). Other errors were scattered through blocks H–S. The distribution of errors in the Alzheimer’s disease group was similar to that in normal controls, although their number was higher. Most errors occurred in block T, others were scattered between blocks E and S. In the MND group, the number of errors also depended on the difficulty of the task, with the first errors occurring already in single word comprehension. A comparison of the single word comprehension of nouns, verbs and adjectives (blocks A, B and C) showed, however, that the errors were not equally distributed in the three blocks: one MND patient made a single error on block A (nouns), a different patient made two errors on block C (adjectives), but all MND patients made at least one error on block B (verbs). None of the controls or the Alzheimer’s disease patients made an error on this block. Subsequently, the number of errors increased with the complexity of the tasks. An exception was seen in block Q (‘not only X, but also Y’), where the correct answer does not require complex semantic cues.

**Noun and verb naming**

Only three patients (Cases 3, 5 and 6) were able to complete the naming task, the last (Case 6) on two consecutive testing rounds. The results are presented in Table 2. The naming of both nouns and verbs was significantly lower in the MND group than in control subjects (Mann–Whitney U test, \( P < 0.0001 \) for nouns and \( P < 0.0001 \) for verbs). There was also a significant difference between MND and Alzheimer’s disease patients for both categories (Mann–Whitney U test, \( P = 0.007 \) for nouns and \( P = 0.006 \) for verbs). In all MND patients, however, the naming of nouns was better than that

### Table 2 Results of TROG, noun and verb naming and comprehension in MND patients, Alzheimer’s disease patients and controls

<table>
<thead>
<tr>
<th></th>
<th>MND</th>
<th>Alzheimer’s disease</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>TROG Total score</td>
<td>54.7 (20)</td>
<td>30–86</td>
<td>94.7 (5.5)</td>
</tr>
<tr>
<td>Nouns</td>
<td>57.5 (15.5)</td>
<td>35–70</td>
<td>87 (16.6)</td>
</tr>
<tr>
<td>Verbs</td>
<td>31.3 (22.9)</td>
<td>5–55</td>
<td>83.8 (17.9)</td>
</tr>
<tr>
<td>Comprehension Nouns</td>
<td>86.1 (12)</td>
<td>60–100</td>
<td>98 (5.7)</td>
</tr>
<tr>
<td>Verbs</td>
<td>62.6 (12)</td>
<td>50–83</td>
<td>96.8 (3.7)</td>
</tr>
</tbody>
</table>

All results show the percentage of correct answers.
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of verbs, although in view of the small size of the group this tendency just failed to reach significance level (Wilcoxon matched pairs test, $P = 0.067$). This difference was maintained in the second testing round of Case 6 (Fig. 8). There was no difference between noun and verb naming in Alzheimer’s disease patients (Wilcoxon matched pairs test, $P = 0.163$) and control subjects (Wilcoxon matched pairs test, $P = 0.345$).

Noun and verb comprehension

All patients were able to complete the comprehension part of the nouns and verbs test, three of them (Cases 1, 2 and 6) on two consecutive occasions. The results are shown in Table 2. While the controls did not produce a single error on either part of this test and Alzheimer’s disease patients performed close to ceiling, an impairment of both noun and verb comprehension was observed in the MND group. There was, in addition, a significant difference between nouns and verbs. Although the MND patients as a group were significantly more impaired in noun comprehension than controls (Mann–Whitney U test, $P < 0.0001$) and Alzheimer’s disease patients (Mann–Whitney U test, $P = 0.0004$), some of them (Cases 1, 2, 3 and 5) performed similarly to the Alzheimer’s disease patients, obtaining 95–100% correct answers (Fig. 8). Moreover, none of the MND patients reached the chance level of 50%. In contrast, the performance on verb naming was significantly worse in the MND group, compared with controls (Mann–Whitney U test, $P = 0.000$) and Alzheimer’s disease patients (Mann–Whitney U test, $P < 0.0001$); none of the patients scored within the normal limits and two (Cases 1 and 6) performed at chance level. In all patients the percentage of correctly selected verbs was lower than that of nouns and the difference was significant (Wilcoxon matched pairs test, $P = 0.007$). In contrast, there was no significant difference between nouns and verbs in Alzheimer’s disease patients (Wilcoxon matched pairs, $P = 0.0754$) and controls (100% for both). In the patients tested twice (Cases 1, 2 and 6), the difference between nouns and verbs remained pronounced in the second session, despite overall deterioration (Fig. 8).
Discussion

Our report confirms the association of MND with aphasia, as described previously (Caselli et al., 1993; Doran et al., 1995). MND–aphasia can occur both with and without other features of frontotemporal dementia; of our six patients, four had florid changes in personality and behaviour, but two remained purely aphasic. The presence of more global dementia does not appear to influence the linguistic features that were characterized by a progressive reduction in verbal output and a profound breakdown of syntactic processing, affecting both production and comprehension. The impaired language production is illustrated by the written descriptions of the Boston Cookie Theft picture and the comprehension deficit is clearly reflected in the TROG results. Both point to a genuine aphasia, not accountable for by other cognitive, psychiatric or motor symptoms. More detailed analysis reveals a selective deficit in verb processing. In view of recent neurolinguistic evidence for the importance of frontostriatal circuits in verb impairment (Daniele et al., 1994; Cappa et al., 1998), this finding supports the crucial role of the anterior structures of the language system in verb processing. The results are strengthened further by the post-mortem findings, showing pathological changes in the BA 44 (Broca’s area) and 45 (immediately anterior to Broca’s area).

Compared with the extensive literature on MND–dementia (Brion et al., 1980; Hudson, 1981), which has established the frequency and pattern of cognitive deficits found in this syndrome (Neary et al., 1990; Talbot et al., 1995; Rakowicz and Hodges, 1998), the number of reported cases of MND–aphasia remains very small, and the information given is fragmentary (Caselli et al., 1993; Doran et al., 1995). Although this might reflect the relative rarity of this condition, it is likely that language changes are overlooked because of the patient’s dysarthria or accompanying behavioural abnormalities that have greater social sequelae with job loss, breakdown of families or even admission to a psychiatric unit (see Case 1). In support of this suggestion, a study of 19 unselected patients with MND in a district general hospital revealed major cognitive deficits in three, and aphasic symptoms without dementia in two of the patients (Rakowicz and Hodges, 1998). Our study confirms the heterogeneity of MND–aphasia in this respect: four patients (Cases 1, 3, 5 and 6) presented with classical ‘frontal’ features (as delineated in Neary et al., 1990) in addition to their language disorder. In contrast, two patients (Cases 2 and 4) showed no behavioural abnormalities until the very final stages of their disease. Thus, MND–aphasia is often, but not always, associated with features of frontal dementia, which is so characteristic of MND–dementia. The latter is, however, frequently accompanied by language abnormalities, even if the severity does not justify the use of the term ‘aphasia’ (Brion et al., 1980; Mitsuyama, 1984; Neary et al., 1990). In view of the present evidence, both syndromes can be best viewed as extremes of a nosological continuum with a varying degree of overlap between them.

The neurological features, which included fasciculation, wasting and dysphagia, and an EMG pattern suggestive of denervation and the pathological changes in the brain and spinal cord, including anterior horn cell loss particularly in the cervical and thoracic spine, were not distinguishable from those seen in the ‘classical’ form of MND. Consistent with the predominantly bulbar presentation, which has been a frequently described feature of MND–dementia (Hudson, 1981; Talbot et al., 1995), all patients on whom a post-mortem was conducted showed changes in the hypoglossal nucleus in the brainstem. In contrast to those of Doran and colleagues (Doran et al., 1995), our observations suggest that MND–aphasia is more typically a subform of the classical MND rather than a separate entity. The structural (CT/MRI) and functional (SPECT) imaging demonstrated either left-sided, or bilateral, atrophy or hypoperfusion, affecting mainly frontal and temporal lobes. The fact that the degree of atrophy on neuroimaging (and even on the pathological examination) was relatively mild in comparison with the severity of clinical presentation can be explained by the speed of the disease process: in all three cases the time between the occurrence of the first symptoms and death was <3 years.

In the early stages of MND–dementia (represented in our study by Case 5), spontaneous language output is progressively reduced, but not qualitatively changed, in that paraphasic and paragrammatic errors are absent. The other end of the spectrum is represented by Case 4, who at the time of testing was completely mute, so that no analysis of language production could be performed. Cases 1 and 2 represent an intermediate position: although at the time of their first examination they had hardly any spoken language, they did communicate through writing, allowing us a limited assessment of their language production. Written descriptions of the Boston Cookie Theft picture (Goodglass and Kaplan, 1983) showed a dramatic collapse of the syntactic processing characterized by paragrammatisms, perseverations and neologisms in a form almost reminiscent of jargon aphasia in one case and by reduced, agrammatic constructions in the other (Fig. 1). A few weeks later, both patients ceased to write. It is likely that these language samples represent a not uncommon, but short, phase in the development of MND–aphasia, frequently missed due to the rapid decline of most patients.

An aphasic syndrome characterized by massive reduction in spontaneous speech, but comparatively well-preserved confrontation naming, sometimes referred to as ‘dynamic aphasia’, has been repeatedly associated with a disorder of frontal aspects of language production (Luria, 1947; Costello and Warrington, 1989; Cipolotti et al., 1991; Snowden et al., 1996; Robinson et al., 1998). Considering the frontal nature of cognitive impairment in MND–dementia, a similar constellation might be expected to occur. Our results cannot be explained purely by an ‘adyynamic’ component. Those patients with no spontaneous speech (Cases 1, 2 and 4) were also unable to produce single words on confrontation naming. Patients with less severe language production deficits
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(Cases 3, 5 and 6), showed mild but definitive anomia. This anomia was more pronounced for verbs than for nouns, but the difference failed to reach statistical significance because of the small group size.

In view of the difficulties in the assessment of language production in MND–aphasia, the evaluation of comprehension naturally assumes a crucial role in our understanding of the linguistic deficit underlying this syndrome. The literature on MND–dementia provides conflicting evidence, from descriptions of fully intact language comprehension (Peavy et al., 1992) to the reports of moderate or severe deficits (Mitsuyama, 1984). A similar situation exists in the literature on language in non-demented MND patients. The generally maintained position has been that of intact comprehension. Even Talbot and colleagues, who found significantly impaired performance on the Token Test, argued that this result was due to attentional problems rather than to a primary linguistic disorder (Talbot et al., 1995). In a disease dominated by behavioural changes with perseverations as well as severe dysarthria and mutism, comprehension deficits might often be misattributed to articulatory, general cognitive or motivational problems and overlooked unless formally tested. They have, however, a major impact on the patient’s everyday life, and a test of language comprehension should form, therefore, an integral part of the clinical assessment in MND–dementia.

Our results using a theoretically motivated test of syntactic comprehension, the TROG, confirmed the presence of significant impairment in all patients and showed that the number of errors depended on the syntactic complexity, rather than on sentence length, pointing to a syntactic rather than an attentional or mnemonic deficit as the crucial factor. The degree of the comprehension deficit mirrored that of the language production: the best results were obtained from Case 5, who also showed the smallest reduction in verbal output. In both patients who were tested twice, the decline in the TROG results paralleled that of the general performance. Qualitative evaluation of TROG results demonstrated a pattern of impairment different to that seen in Alzheimer’s disease. It was particularly noticeable that the patients shared a greater number of errors on the comprehension of single verbs (block B) than on comprehension of nouns and adjectives (blocks A and C). In fact, single verb comprehension was more impaired than that of syntactically more complex two-word combinations (blocks D and E). This was confirmed through the separate testing of noun and verb single word comprehension; all six patients made more errors on verbs than nouns, with the effect remaining consistent on consecutive testing. These findings strongly suggest a central breakdown in verb processing.

Noun–verb dissociations, although well documented in psycholinguistic literature (Caramazza and Hillis, 1991; Damasio and Tranel, 1993), can be influenced by different confounding variables. It has been repeatedly pointed out that in most languages verbs tend to be inherently more difficult than nouns due to their greater grammatical complexity. This is certainly the case in English and Italian, in which most noun–verb dissociation studies have been conducted (although less so in languages with complex noun morphology such as Greek or most Slavonic languages). Since our controls performed at ceiling level for both nouns and verbs we decided to include a second control group of Alzheimer’s disease patients. Within the domain of language, the most consistent deficits in Alzheimer’s disease involve semantic processing and word retrieval (Hodges and Patterson, 1995), although subtle syntactic deficits can also be found (Croft et al., 1999). Studies attempting to elucidate specific word class effects in Alzheimer’s disease have produced contradictory results, with some showing greater involvement of verbs and others the opposite pattern (Devine et al., 1995; Grossman et al., 1996; Robinson et al., 1996). In frontotemporal dementia, the only study to date examining word class specific deficits has shown a much greater impairment of verb processing (Cappa et al., 1998). Our finding of a difference between noun and verb comprehension in MND–aphasia, but not in Alzheimer’s disease patients speaks, therefore, in favour of a genuine verb impairment in this syndrome. Berndt and colleagues, using the same tasks as the one used in the present study, have documented selective impairment of both noun and verb processing, a result not accounted for by differences in frequency or difficulty (Berndt et al., 1997). An additional confounding variable taken into account was visual complexity. Since visuospatial perception was invariably well preserved in all patients, breakdown in this domain is an unlikely explanation for the observed pattern of verb impairment. Future studies using more sensitive tests will be required to determine whether the verb impairment is confined to MND–aphasia and MND–dementia or whether it can be detected in a milder form in non-demented MND patients. If so, a test of noun and verb processing might develop into a useful tool for detecting early cognitive impairment in MND.

Throughout this article we have used the words ‘nouns’ and ‘verbs’ to describe the difference between the two types of pictures used for naming and comprehension tasks. This distinction could also be described as ‘objects’ versus ‘actions’. The tests used in our study, like most tests reported in the literature, cannot distinguish between the semantic (objects versus actions) and syntactic (nouns versus verbs) categories. Our results could, therefore, be interpreted as a selective deficit in naming and comprehension of actions rather than in that of verbs. These aspects are, however, very closely interrelated. Some linguists, particularly those working in the framework of functional linguistics (Givon, 1984; Langacker, 1987), interpret the syntactic categories of verbs and nouns as a functional consequence of their semantic difference. The semantic difference between objects and actions might ultimately be related to motor and sensory systems in the brain. Possible links between the motor function and different subsystems of language processing (particularly the dichotomy between rule-based grammar versus memory-based lexicon) were postulated recently by
Ullman and colleagues (Ullman et al., 1997), MND, with its predominant impairment of the motor system, offers an important theoretical insight into these questions, although the severity and rapidity of the disease make extensive testing extremely difficult.

Apart from general changes characteristic for MND (ventral root atrophy, neuronal loss in the spine and in the hypoglossus nucleus), the pathological examination revealed consistent changes (mainly microvacuolation) in the BA 44 and 45. The importance of BA 44 (opercular part of Broca’s area) for language production has been recognized since the late 19th century, but its exact role in language processing remains controversial. Traditionally associated with the clinical picture of agrammatism, it has recently been discussed in the context of mental stimulation of hand actions (Decety et al., 1994), the generation of action verbs (Martin et al., 1995) and phonological processing (Paulesu et al., 1997). Brodmann area 45 has also been implied in verb retrieval (Warburton et al., 1996) and spontaneous speech production in a case of dynamic aphasia (Robinson et al., 1998). In a recent neuroimaging study using PET, both areas were activated in a lexical decision task for verbs as opposed to nouns (Perani et al., 1999). The present study adds histopathological evidence to these clinical and neuroimaging data. Several questions remain to be answered. If BA 44 and 45 have a central role in verb processing, it is not clear why a verb deficit is not a consistent finding in all patients with lesions of this region. Such a deficit could be masked by more general linguistic deficits, affecting other aspects of speech. It could also be dependent on a specific subregion. Detailed clinico-pathological studies of neurodegenerative diseases in general, and MND–aphasia in particular, might offer an important contribution to our understanding of specific word class effects and their neural correlates.

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Appendix
The blocks of the TROG
A. Single noun, e.g. ‘shoe’
B. Single verb, e.g. ‘eating’
C. Single adjective, e.g. ‘long’
D. Two element combination, e.g. ‘the boy is running’
E. Negative, e.g. ‘the boy is not running’
F. Three element combination, e.g. ‘the boy is jumping over the box’
G. Singular/plural personal noun, e.g. ‘they are sitting on the table’
H. Reversible active, e.g. ‘the girl is pushing the horse’
I. Masculine/feminine personal pronoun, e.g. ‘she is sitting on the chair’
J. Singular/plural noun inflection, e.g. ‘the cats look at the ball’
K. Comparative/absolute, e.g. ‘the knife is longer than the pencil’
L. Reversible passive, e.g. ‘the girl is chased by the horse’
M. In and on, e.g. ‘the cup is in the box’
N. Post-modified subject, e.g. ‘the boy chasing the horse is fat’
O. X but not Y, e.g. ‘the box but not the chair is red’
P. Above and below, e.g. ‘the pencil is above the flower’
Q. Not only X but also Y, e.g. ‘not only the bird but also the flower is blue’
R. Relative clause, e.g. ‘the pencil is on the book that is yellow’
S. Neither X nor Y, e.g. ‘neither the dog nor the ball is brown’
T. Embedded sentence, e.g. ‘the book the pencil is on is red’