

The effects of motor neurone disease on language: Further evidence

Thomas H. Bak^{a,b} and John R. Hodges^{a,b,*}

^a *Medical Research Council—Cognition and Brain Sciences Unit, Cambridge, UK*

^b *The University of Cambridge Neurology Unit, Addenbrooke's Hospital, Cambridge, UK*

Accepted 26 August 2003

Abstract

It might sound surprising that Motor Neurone Disease (MND), regarded still by many as the very example of a neurodegenerative disease affecting selectively the motor system and sparing the sensory functions as well as cognition, can have a significant influence on language. In this article we hope to demonstrate that language dysfunction is not only a pronounced and well documented symptom in some MND patients but also that the study of language in MND can address interesting theoretical questions about the representation of language and conceptual knowledge in the brain. After a brief introduction delineating clinical and pathological features of the disease we discuss the evidence available in the literature for language dysfunction in MND. We then present linguistic data from our own study of seven patients with MND/dementia/aphasia syndrome focusing on the dissociation between noun and verb processing. To illustrate the clinical, neuropsychological and linguistic aspects of MND we describe in more detail the patient E.N., a pathologically confirmed case of MND/dementia. Finally, we attempt to characterise the nature of the linguistic impairment in MND in the light of current debates about the mechanisms underlying noun/verb dissociation.

© 2003 Elsevier Inc. All rights reserved.

Keywords: Motor neurone disease; Frontotemporal dementia; Language; Aphasia; Verb impairment

1. Language involvement in motor neurone disease: Past evidence and future perspectives

One fundamental limitation to neuropsychological lesion studies in humans is the fact that, in many traditionally investigated conditions, the type and extent of brain damage is determined primarily by the lesion location (e.g., arterial territories in stroke, the site of the injury in trauma or the site of the tumour in neoplasms), which bears often little relation to the functional architecture of the underlying brain regions. Neighbouring areas of different embryological origin, with different functions and diverging patterns of connectivity can be affected in the same way. The broad and heterogeneous group of neurodegenerative diseases offers a different approach to the study of the relationship between brain structure and function. In contrast to strokes or tumours, many neurodegenerative conditions can be interpreted as system degenerations, affecting distant parts

of the nervous system that are linked to each other functionally via long-distance connections rather than by their topographical proximity. Their study can, therefore, contribute to important insights into the functioning of the brain.

Motor Neurone Disease (MND)¹ is a progressive neurodegenerative condition affecting selectively parts of the nervous system involved in planning and execution of movements. Pathological changes can be found in different, often distant parts of the nervous system related to movement, from motor areas of the cerebral cortex, through brainstem (e.g., nucleus of the XII cranial nerve, the hypoglossus) to the anterior horn cells of the spinal cord. On the other hand, neighbouring anatomical structures involved in other (e.g., sensory) functions remain largely unaffected. In recent years ubiquitin-positive inclusions have been reported in a

¹ The terms Motor Neurone Disease (MND) and Amyotrophic Lateral Sclerosis (ALS) are often used interchangeably, the former mainly in Britain, the latter in continental Europe and North America. Strictly speaking, however, MND is a broader term encompassing ALS as well as other related conditions.

* Corresponding author. Fax: +44-1223-359062.

E-mail address: john.hodges@mrc-cbu.cam.ac.uk (J.R. Hodges).

growing number of cases with MND and MND-associated dementia. They can be localised in different parts of the nervous system but involve typically the dentate fascia of the hippocampus (Leigh et al., 1991). Similar changes have been, however, described in patients without any symptoms or signs of MND (Kovari et al., 2000; Rossor, Revesz, Lantos, & Warrington, 2000) and their exact pathological importance remains unknown.

The clinical picture of MND is highly characteristic and combines pyramidal signs such as spastic paresis and brisk reflexes (resulting from the damage to the upper motor neurone) with muscle wasting and fasciculations (pointing to the involvement of the lower motor neurone). The exact distribution of symptoms can vary depending on the focus and extent of pathological changes and can affect upper or lower limbs as well as muscles crucial to breathing and swallowing. The latter are affected in the bulbar form of MND, presenting mainly with dysphagia and dysarthria. The disease has a peak incidence between 50 and 70 years of age and is slightly more common in men (Eisen & Krieger, 1998). Although great variability in disease duration has been reported, the majority of patients die within few years after the onset of the first symptoms. Unfortunately no cure exists at the moment, but some drugs, such as the neuroprotective agent Riluzole, have been reported to slow down the progression of the disease.

Despite the relative predominance of motor symptoms, characteristic changes in personality and behaviour (which in modern terminology would be referred to as frontotemporal dementia² or Pick's disease) and cognitive deficits (described in modern terms as frontal-executive dysfunction) have been also frequently described in MND patients (for reviews see Bak & Hodges, 1999; Bak & Hodges, 2001; Brion et al., 1980; Hudson, 1981). These changes have been associated with frontal atrophy on the structural (Ishikawa, Nagura, Yokota, & Yamanouchi, 1993) and frontal hypoactivation/hypoperfusion on the functional neuroimaging (Abe, Fujimura, & Toyooka, 1993; Kew et al., 1993; Ludolph et al., 1992). In a small, but relatively well described, group of MND patients cognitive and behavioural changes can form the presenting feature (characteristically preceding the development of the classical motor signs by 6–12 months) and dominate the clinical picture until the late stages of the disease (Bak & Hodges, 2001; Neary et al., 1990). The prognosis of these MND/dementia cases is considered to be even worse than that of the classical

MND and the patients rarely survive more than two to three years after presentation.

In comparison with alterations in behaviour and frontal-executive functions, language changes associated with MND have received much less attention. The most frequently mentioned language symptom described in the literature on MND is reduced verbal output, often leading to complete mutism within a few months and referred to as “speechlessness” (van Bogaert, 1925) or “inability to speak” (Ziegler, 1930). In many cases these symptoms precede the development of dysarthria and, therefore, cannot be explained purely in terms of an effortful speech. Although an analysis of written language could provide valuable information about the language production in otherwise mute patients, as yet no systematic study has addressed this issue, apart from a single report of “spelling errors” (Ferrer, Roig, Espino, Peiro, & Guiu, 1991). Another constellation of symptoms, observed in MND patients consists of perseverations, echolalia, and the use of stereotypic expressions (Constantinidis, 1987; Meyer, 1929). It is noteworthy that their non-verbal counterparts (stereotypic movements, echopraxia) are not reported with the same frequency. Despite the emphasis on language production, comprehension is occasionally reported to be affected in some cases of MND/dementia (Deymeer, Smith, DeGirolami, & Drachman, 1989; Mitsuyama & Takamiya, 1979; Neary et al., 1990), although this tends to be attributed to deficits in abstract reasoning or to general dementia rather than to specific syntactic deficits (Neary et al., 1990; Peavy, Herzog, Rubin, & Mesulam, 1992). More overt aphasic symptoms, e.g., “semantic paraphasias” are only seldom reported in MND (Gentileschi, Sperber, & Spinnler, 1999; Neary et al., 1990). Wilkstrom, Paetau, Palo, Sulkava, and Haltia (1982) observed the loss of “command of languages” in a multilingual patient with MND/dementia, but unfortunately no further details were provided.

A full blown aphasia can be associated with MND. Mitsuyama (1984) noticed a “severe dysphasia with poor comprehension” in one of his patients. Tsuchiya et al. (2000) reported a patient with “severe motor aphasia” who “could not understand sentences and phrases.” A more detailed description was provided by Caselli et al. (1993) who presented seven patients in whom progressive non-fluent aphasia was the presenting and dominant feature. Besides the prominent bulbar symptoms with dysarthria, all patients showed evidence of an aphasic component, both in spoken and written language, as well as impaired comprehension. The five patients described by Doran, Xuereb, and Hodges (1995) showed a very similar clinical picture; in three, significant deficits in syntactic comprehension were documented on the shortened version of the Token Test (De Renzi & Faglioni, 1978) and on the Test for the Reception of Grammar (TROG), a sentence–picture matching test examining, in

² The use of capital letters in the names of diseases is not always consistent. Diseases regarded as well established nosological entities, such as MND, are frequently written with capital letters. Terms, which are considered to reflect heterogeneous syndromes, such as frontotemporal dementia or progressive aphasia, are more often written with lower case.

20 separate blocks of 4 sentences each, the comprehension of different syntactic structures from single nouns, verbs and adjectives to comparative, negation and passive constructions as well as embedded sentences (Bishop, 1989). Interestingly, although behavioural, cognitive, and linguistic symptoms may overlap, aphasic symptoms can be found independently of dementia (Rakowicz & Hodges, 1998).

The previously neglected cognitive, behavioural and linguistic aspects of MND are now receiving more recognition among specialists as illustrated by the fact that the most recent international MND meeting dedicated a major symposium to this topic (Annual Meeting of the ALS/MND Association in Melbourne, November 2002, reported in *Amyotrophic Lateral Sclerosis*, Vol. 3, Supplement 2, pp. 13–16). The study of language function in MND presents, however, several difficulties, arising mainly from confounding variables related to other (motor, psychiatric, and cognitive) aspects of the disease:

- (a) MND, particularly in its bulbar presentation, is often associated with dysarthria, which interferes with all tasks involving language production and articulation.
- (b) The behavioural changes described in MND can consist of social withdrawal, apathy and loss of drive, symptoms which can be due to depression as well as to frontotemporal dementia. The reduction in verbal output may have, therefore, psychiatric as well as linguistic reasons.
- (c) Non-linguistic cognitive deficits, such as frontal-dysexecutive syndrome or memory dysfunction, can also contribute to impairment on linguistic tasks.

Future studies of language in MND will have to take these difficulties into account. The linguistic data should be analysed against the broader background of other symptoms. The tests applied should try to minimise the confounding variables, e.g., by employing tests requiring pointing rather than verbal response. Finally, in depth studies of the relatively rare patients with MND/aphasia and MND/dementia should be complemented by larger group studies examining language function in non-demented MND patients.

2. The Cambridge MND/aphasia series

In the years 1996–2002 we had the opportunity to examine seven patients presenting, in a fairly uniform manner, with an insidious onset of predominantly neuropsychiatric symptoms such as obsession with food, overeating, hoarding, “childlike behaviour,” irritability, disinhibition, socially inappropriate behaviour, and, in some cases, paranoid ideas and hallucinations (one of the patients, N.N., believed that her childhood boyfriend, whom she has not seen for decades, moved into

her house). Neurological examination in all patients was normal, apart from positive frontal release signs (including glabellar tap, pout, and grasp reflexes) and difficulty in motor sequencing (such as alternating hand movements). The neuropsychological testing revealed pronounced frontal-executive deficits but remarkably well preserved visuospatial functions (including drawing and copying). In all patients a progressive poverty of spontaneous speech was reported well before the occurrence of dysarthria. On admission the majority of patients were either mute or had a minimal verbal output, but some of them were still able to write and to communicate with gestures.

The language deficits were, however, not confined to speech production. All seven patients were severely impaired on a test of syntactic comprehension, the TROG, not only in comparison to healthy age-matched controls but also to patients with Alzheimer’s disease. Their disproportionately poor performance on the second block of the TROG (single verbs) alerted us to a possible dissociation between noun and verb processing, as described previously in other neurodegenerative diseases such as Progressive Supranuclear Palsy (Daniele, Giustolisi, Silveri, Colosimo, & Gainotti, 1994), frontotemporal dementia (Cappa et al., 1998), and, more recently, non-fluent progressive aphasia (Hillis, Tiffias, & Caramazza, 2002). Indeed, when nouns and verbs were examined separately (using noun and verb naming and comprehension test described in Berndt, Mitchum, & Wayland, 1997), a consistently larger impairment was noticed in verbs on both naming (if possible to test) and comprehension task. This difference remained stable, despite overall deterioration, on repeated testing, and has been described in detail elsewhere (Bak & Hodges, 1997; Bak, O’Donovan, Xuereb, Boniface, & Hodges, 2001).

Also the course of the disease was remarkably similar in all cases. Between 6 and 12 months after occurrence of the first symptoms all patients developed characteristic signs of MND including wasting and fasciculations. The symptoms were most pronounced in the bulbar region, causing dysarthria and dysphagia. The lower limbs, in contrast, were least affected and most patients remained mobile until the final stages of the disease. In all cases the diagnosis was confirmed by electromyography. Imaging (MRI and/or CT) showed mild to moderate degree of frontal lobe atrophy without any other relevant changes.

All seven patients died within three years of the occurrence of the first symptoms, mostly due to aspiration pneumonia resulting from dysphagia. Post-mortem examination was conducted in five patients with remarkably similar results. The brainstem and spinal cord changes were practically indistinguishable from patients with classical MND, but in addition, characteristic cortical changes were observed, including ubiquitin-positive inclusions in the dentate fascia of the hippocampus

and cell loss and spongiosis, particularly pronounced in the Brodmann areas 44 and 45 (Broca's area).

Due to the rapid deterioration of cognitive and bulbar symptoms most patients became untestable before a more detailed assessment could be completed. In one of the patients, however, the initial impairment was slightly less pronounced and the deterioration slower, so that we were able to assess him in more detail. The description of his case will be used, therefore, to illustrate some characteristic features of language impairment in MND.

3. E.N.—Case description

The patient E.N. (initials changed to protect privacy) was admitted to Addenbrooke's Hospital, Cambridge with a clinical picture similar to that of other MND/dementia cases. The history of his illness began one year earlier, when his wife noticed persecutory delusions and a change in food preference (towards chocolate and peanuts). Over the following four to five months the patient became slower, his speech slurred and his verbal output extremely limited (usually "yes" and "no"). His cognitive decline had accelerated in the few weeks preceding his hospital admission. On examination he had mild extrapyramidal features such as bradykinesia (slowness of movements) and increased muscle tone in the limbs, which could be explained as possible side-effects of the medication with Olanzapine, prescribed to control his delusions. He also had positive frontal release signs, mild dyspraxia and difficulty performing alternating hand movements. The MRI showed atrophy of the frontal lobes with relatively well preserved medial temporal and posterior aspects of the brain; the SPECT revealed bilateral frontal hypoperfusion. On cognitive assessment he was impaired on the majority of tests and scored below the cut-off score on several cognitive screening tests: 22/30 on the Mini Mental State Exam MMSE (Folstein, Folstein, & McHugh, 1975), 52/100 on the Addenbrooke's Cognitive Examination ACE (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000) and 87/144 on the Dementia Rating Scale DRS (Mattis, 1988). The deficits were most pronounced in frontal-executive functions, e.g., his verbal fluency was 2–4/min for categories, 0–1/min for letters. In contrast, he achieved his relatively best results on visuospatial tasks: he scored 6/6 on the construction subtest of the DRS and passed several subtests of the Visual Object and Space Perception Battery VOSP (including an incomplete letter, object decision, and cube analysis) (Warrington & James, 1991). This frontal pattern of impairment can explain the finding of a borderline score on the MMSE, a test largely insensitive to frontal dysfunction, while his performance on more comprehensive cognitive screening tests (ACE, DRS) yielded results well below the normal range.

Although no motor neurone signs were detectable on admission, the fast rate of progression raised the suspicion of MND/dementia. Diagnostic electromyography was in keeping with the diagnosis of MND and within the next three months the patient developed wasting and fasciculations. On follow up assessment six months later he had no verbal output but was still able to communicate through facial expression, gesture, and pointing. It is remarkable that he was still able to perform tasks requiring drawing, scoring again 6/6 on the construction subtests of the DRS. His decline continued, however, at a fast rate and he died in January of the following year, less than two years after the appearance of the first symptoms. A post-mortem examination confirmed the diagnosis of MND. Ubiquitin-positive inclusions were found in the dentate fascia of the hippocampus. The pathological changes in the frontal cortex were similarly distributed (affecting Brodmann areas 44 and 45), although less pronounced, than in the other cases described above.

In contrast to our previous MND/dementia/aphasia patients, in whom only a very brief assessment could be completed before the rapid deterioration rendered them untestable, in the case of E.N. we were able to collect some more detailed neuropsychological, and particularly language related, data. The patient's comprehension of syntactically complex sentences (as measured by the TROG) was moderately impaired on his initial testing and dropped further on the follow-up assessment (Table 1). His comprehension of simple nouns and verbs was at ceiling on the first testing round, with a minimal drop in verb comprehension on the second round. Verb naming was more impaired than noun naming on the first testing round but the difference did not reach significance (all normal controls performed at ceiling on both naming and comprehension part of this test). On the second testing round the patient was already mute and the assessment of naming was no longer possible.

We were able, however, to perform an additional test of action knowledge processing: the Kissing and Dancing Test (KDT). This test has been developed to complement the Pyramids and Palmtrees Test (PPT, (Howard & Patterson, 1992), which examines the association between objects based on picture matching task and allows testing of semantic knowledge in a way which does not require either comprehension or

Table 1
Results of the patient E.N. on naming and comprehension tasks (in percentage correct)

	TROG	Noun comp.	Verb comp.	Noun nam.	Verb nam.
March 2000	76	100	100	70	55
October 2000	66	100	90	—	—

On the second round the patient was not able to perform any naming tasks.

Comp, comprehension; Nam, naming.

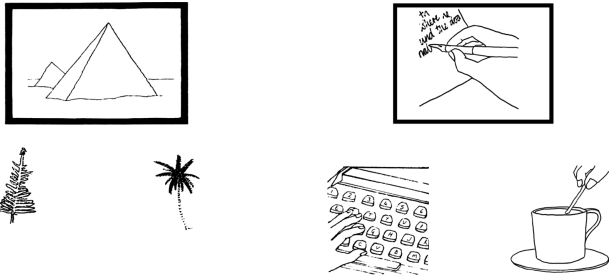


Fig. 1. An example of a picture triplet from Pyramid and Palmtrees Test (PPT, left) and Kissing and Dancing Test (KDT, right)

production of words. The PPT consists of 52 triplets of pictures depicting different objects. The task consists in selecting the better matching picture, e.g., pyramids can be associated with palm trees rather than with fir trees (see Fig. 1, left). The KDT was constructed to match PPT as closely as possible in form, size, design, test instructions, and scoring procedure. Like PPT it also consists of 52 triplets of pictures, but in contrast to the PPT they depict actions rather than objects. Writing, for instance, is considered to be more closely related to typing than to stirring (see Fig. 1, right). The PPT and KDT administered in conjunction, were validated in 30 healthy controls. No significant difference was found between the performance on the two tasks, with controls scoring between 49 and 52/52 on both. The tests were also able to detect a contrasting pattern of impairment in a group of patients consisting of the frontal variant of frontotemporal dementia (fvFTD) and semantic dementia (SD): the former were more impaired on KDT, the latter on PPT (Bak & Hodges, 2003).

By the time the KDT had been developed the majority of our MND/aphasia patients were already untestable. We were able, however, to examine three patients: L.N. with the preliminary (containing 40 items

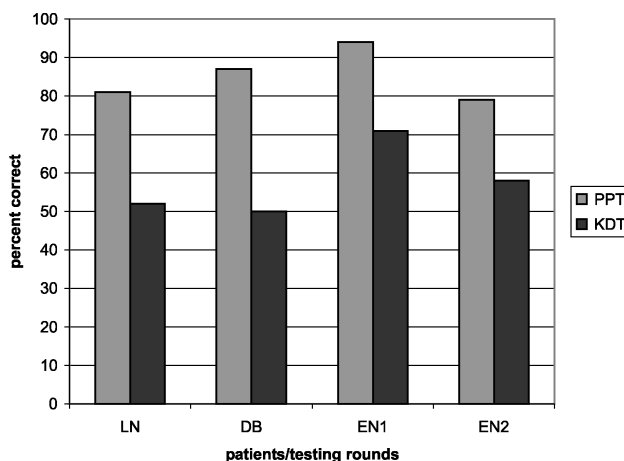


Fig. 2. Results of the patients L.N., D.B., and E.N. (first and second testing round) on the Pyramid and Palmtrees Test (PPT) and Kissing and Dancing Test (KDT) in percentage correct.

only), D.B. and E.N. with the final (52 items) version of the test. Their results are shown in Fig. 2. As can be seen, all patients had a significantly worse performance on KDT in comparison to PPT (χ^2 8.37 for L.N., 16.02 for D.B., $p < .01$). Patient E.N. was the first MND case in whom we were able to obtain longitudinal data on PPT and KDT. On the first testing round E.N.'s performance on PPT was still just within the normal range while his KDT result was clearly impaired (χ^2 9.67, $p < .01$). On the follow-up assessment his scores deteriorated on both tests but the difference between them remained virtually the same—the KDT on that occasion was close to chance level (χ^2 5.37, $p = .02$).

4. Discussion: Towards a better characterisation of the linguistic deficit in MND

Our findings confirm that aphasia can be an early and prominent feature of MND/dementia. Pronounced language dysfunction was documented in all seven examined patients. In all cases it preceded the development of motor symptoms and was, therefore, unlikely to be caused by them. It is equally unlikely that the language dysfunction was a result of generalised dementia: the level of language impairment was much higher than would be expected on the basis of the results on cognitive screening tests. Moreover, some cognitive domains such as visuospatial functions remained relatively well preserved. Finally, the spontaneous employment by some patients of non-verbal means of communication such as gesturing, pointing, drawing or writing demonstrated that the reduction in verbal output cannot be explained in terms of apathy or withdrawal. Since previous descriptions of MND/dementia rarely contained a detailed language assessment (Bak & Hodges, 2001) it is difficult to determine whether this high prevalence of language changes was specific to this particular patient group or whether it constitutes a common but underrecognised feature of the clinical picture of MND/dementia. Only a large, systematic study, including a comprehensive linguistic, as well as general cognitive assessment will be able to clarify the relationship between aphasia and dementia associated with MND.

Characteristically, in all patients the level of impairment was higher for verbs than for nouns, both in production and in comprehension tasks. An opposite pattern of greater noun than verb impairment was never observed in this patient group. In the three patients in whom PPT and KDT were tested in conjunction, the performance on KDT (matching of pictures depicting actions) was consistently worse than on PPT (object matching). In the patient E.N., the only one who was tested twice, the difference remained stable despite overall deterioration. This result is consistent with a

broader interpretation of the verb deficit in MND, which is not confined to the lexical level but encompasses also the abstract representations of actions.

Selective deficits in processing of nouns and verbs have been recognised for centuries (Linnaeus, 1745; Vico, 1744), but their interpretation remains controversial. Some authors interpret them as evidence for separate neural systems underlying different word classes (Hillis et al., 2002), while others focus on semantic differences linking verbs to actions and nouns to sensory, mainly visual, processing of objects (Bredin, Saffran, & Schwartz, 1998). Although both views might seem mutually exclusive they could well be reconciled within the framework of a linguistic theory in which the syntactic characteristics of nouns and verbs are derived from their functional attributes (Givon, 1984).

In anatomical terms, verb deficits have been linked to frontal, and noun deficits to temporal, pathology (Cappa et al., 1998; Daniele et al., 1994). Selective verb impairment has been demonstrated in frontotemporal dementia (Cappa et al., 1998) and in primary progressive aphasia (Hillis et al., 2002). By contrast, patients with semantic dementia show more pronounced impairment in object processing (Bak & Hodges, 2003). The strong evidence associating MND/dementia with frontal lobe involvement provides a link between MND and other forms of FTD. The majority of our patients had frontal atrophy on MRI and/or frontal hypoperfusion on SPECT. Degeneration of the frontal lobes was also confirmed on the pathological examination (the comparatively mild degree of atrophy in comparison to the severity of symptoms can be explained by the fast rate of progression). Frontal pathology, particularly involving Brodmann areas 44 and 45 could, therefore, explain the observed verb impairment.

But why are the frontal lobes more involved in MND/dementia than any other cortical structures? And why is MND so consistently associated with FTD, rather than with more diffuse cortical pathology as in Alzheimer's disease or a subcortical dementia of the type described in basal ganglia diseases such as Parkinson's Disease and Progressive Supranuclear Palsy? A possible answer to these questions is that the same principle of selectivity, which leads to the predominant dysfunction of the motor and relative sparing of the sensory systems in MND, is also responsible for the stronger involvement of actions (and verbs as their linguistic correlates) than of objects in the cognitive variant of this disease. An additional support for this view comes from recent findings demonstrating an association between verb processing and motor function in studies of healthy volunteers using sophisticated neurophysiological methods such as high resolution EEG and event-related brain po-

tentials (Pulvermüller, Härle, & Hummel, 2000; Pulvermüller, Lutzenberger, & Preiss, 1999). Clearly, larger and more detailed studies are needed to address this question. It remains to be established whether a selective verb and action impairment can be observed only in the full-blown cases of MND/dementia or whether more subtle deficits can be detected in non-demented patients. Changes of frontal-executive function have been described in MND patients without dementia (Ludolph et al., 1992) suggesting a continuum between the cognitively impaired and cognitively preserved forms of the disease (Bak & Hodges, 2001). Language function in general and noun/verb dissociation in particular has not, however, been studied in detail in this patient group. If the finding of a selective verb deficit can be confirmed in a larger number of patients, MND could become a valuable model for the study of the interrelation between movement, language, and cognition.

Acknowledgments

We thank Tina Emery and Angela O'Sullivan for their dedicated work and their support for our patients and their families in general and E.N. in particular. We are indebted to John Xuereb and the Cambridge Brain Bank for the pathological examination of the brains of MND patients, to Simon Boniface for the neurophysiological assessment, to Karalyn Patterson and Friedemann Pulvermüller for many fruitful discussions and to Marion Wilkinson and Ashley Muir for their help in editing the manuscript. We also acknowledge the contribution of Rita Berndt, Judit Druks and Jackie Masterson, who allowed us to use and to adapt their testing materials in order to develop the Kissing and Dancing Test. Finally, Brian Cox helped with the graphic design of the test.

References

- Abe, K., Fujimura, H., & Toyooka, K. (1993). Single-photon emission computed tomographic investigation of patients with motor neuron disease. *Neurology*, *43*, 1569–1573.
- Bak, T., & Hodges, J. R. (1997). Noun–verb dissociation in three patients with motor neuron disease and aphasia. *Brain and Language*, *60*, 38–40.
- Bak, T., & Hodges, J. R. (1999). Cognition, language and behaviour in motor neurone disease: Evidence of frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders*, *10*, 29–32.
- Bak, T., & Hodges, J. R. (2001). Motor neurone disease, dementia and aphasia coincidence, co-occurrence or continuum? *Journal of Neurology*, *248*(4), 260–270.
- Bak, T., & Hodges, J. R. (2003). “Kissing and Dancing—A test to distinguish the lexical and conceptual contributions to noun/verb and action/object dissociation. Preliminary results in patients

- with frontotemporal dementia. *Journal of Neurolinguistics*, 16, 169–181.
- Bak, T. H., O'Donovan, D. G., Xuereb, J. H., Boniface, S., & Hodges, J. R. (2001). Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease–dementia–aphasia syndrome. *Brain*, 124, 103–120.
- Berndt, R., Mitchum, C., & Wayland, S. (1997). Patterns of sentence comprehension in aphasia: A consideration of three hypotheses. *Brain and Language*, 60, 197–221.
- Bishop, D. V. M. (1989). *Test for the reception of grammar* (2nd ed.). London: Medical Research Council.
- Breedin, S., Saffran, E., & Schwartz, M. (1998). Semantic factors in verb retrieval: An effect of complexity. *Brain and Language*, 63, 1–31.
- Brion, S., Psimaras, A., Chevalier, J. F., Plas, J., Massa, G., & Jatteau, O. (1980). L'association maladie de Pick et sclerose laterale amyotrophique. *Encephale*, 6, 259–286.
- Cappa, S. F., Binetti, G., Pezzini, A., Padovani, A., Rozzini, L., & Trabucchi, M. (1998). Object and action naming in Alzheimer's disease and frontotemporal dementia. *Neurology*, 50, 351–355.
- Caselli, R. J., Windebank, A. J., Petersen, R. C., Komori, T., Parisi, J. E., Okazaki, H., Kokmen, E., Iverson, R., Dinapoli, R. P., Graff-Radford, N. R., & Stein, S. D. (1993). Rapidly progressive aphasic dementia and motor neuron disease. *Annals of Neurology*, 33, 200–207.
- Constantinidis, J. (1987). Syndrome familial: Association de Maladie de Pick at sclerose laterale amyotrophique. *Encephale*, 13, 285–293.
- Daniele, A., Giustolisi, L., Silveri, M. C., Colosimo, C., & Gainotti, G. (1994). Evidence for a possible neuroanatomical basis for lexical processing of nouns and verbs. *Neuropsychologia*, 32, 1325–1341.
- De Renzi, E., & Faglioni, P. (1978). Normative data and screening power of a shortened version of the Token Test. *Cortex*, 14, 41–49.
- Deymeer, F., Smith, T. W., DeGirolami, U., & Drachman, D. A. (1989). Thalamic dementia and motor neuron disease. *Neurology*, 38(January), 58–61.
- Doran, M., Xuereb, J., & Hodges, J. R. (1995). Rapidly progressive aphasia with bulbar motor neurone disease: A clinical and neuropsychological study. *Behavioural Neurology*, 8, 169–180.
- Eisen, A., & Krieger, C. (1998). *Amyotrophic Lateral Sclerosis: A synthesis of research and clinical practice*. Cambridge: Cambridge University Press.
- Ferrer, I., Roig, C., Espino, A., Peiro, G., & Guiu, M. (1991). Dementia of frontal lobe type and motor neuron disease. A Golgi study of the frontal cortex. *Journal of Neurology, Neurosurgery, and Psychiatry*, 54, 932–934.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Minimal state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189–198.
- Gentileschi, V., Sperber, S., & Spinnler, H. (1999). Progressive defective recognition of familiar people. *Neurocase*, 5, 407–423.
- Givon, T. (1984). *Syntax: Functional-typological introduction*. Amsterdam: John Benjamins.
- Hillis, A. E., Tiffash, E., & Caramazza, A. (2002). Modality-specific deterioration in naming verbs in nonfluent primary progressive aphasia. *Journal of Cognitive Neuroscience*, 14, 1099–1108.
- Howard, D., & Patterson, K. (1992). *Pyramids and palm trees: A test of semantic access from pictures and words*. Bury, St. Edmunds, Suffolk: Thames Valley Test Company.
- Hudson, A. J. (1981). Amyotrophic lateral sclerosis and its association with dementia, Parkinsonism and other neurological disorders: A review. *Brain*, 104, 217–247.
- Ishikawa, K., Nagura, H., Yokota, T., & Yamanouchi, H. (1993). Signal loss in the motor cortex on magnetic resonance images in amyotrophic lateral sclerosis. *Annals of Neurology*, 33, 218–222.
- Kew, J. J. M., Leigh, P. N., Playford, E. D., Passingham, R. E., Goldstein, L. H., Frackowiak, R. S. J., & Brooks, D. J. (1993). Cortical function in amyotrophic lateral sclerosis. *Brain*, 116, 655–680.
- Kovari, E., Leuba, G., Savios, A., Saini, K., Anastasiu, R., Miklossy, J., & Bouras, C. (2000). Familial frontotemporal dementia with ubiquitin inclusion bodies and without motor neuron disease. *Acta Neuropathologica*, 100, 421–426.
- Leigh, P., Whitwell, H., Garofalo, O., Buller, J., Swash, M., Martin, J. E., Gallo, J., Weller, R., & Anderton, B. (1991). Ubiquitin-immunoreactive intraneuronal inclusions in amyotrophic lateral sclerosis. Morphology, distribution and specificity. *Brain*, 114, 775–788.
- Linnaeus, C. (1745). Glömska of alla Substantiva och i synnerhet namn (translated as Amnesia for all nouns, proper names in particular by P Ostberg). Kungl. Svenska Vetenskaps - Akademiens Handlingar (Transactions of the Royal Swedish Academy of Sciences), April, 116–117.
- Ludolph, A. C., Langen, K. J., M, R., Herzog, H., Kemper, B., Kuwert, T., Bottger, I. G., & Feinendegen, L. (1992). Frontal lobe function in amyotrophic lateral sclerosis: A neuropsychological and positron emission tomography study. *Acta Neurologica Scandinavica*, 85, 81–89.
- Mathuranath, P. S., Nestor, P., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, 55, 1613–1620.
- Mattis, S. (1988). *Dementia rating scale*. Windsor: NFER-Nelson.
- Meyer, A. (1929). Über eine der amyotrophischen Lateralsklerose nahestehende Erkrankung mit psychischen Störungen. Zugleich ein Beitrag zur Frage der spastischen pseudosklerose (A. Jakob). *Zeitschrift für die Gesamte Neurologie und Psychiatrie*, 121, 107–128.
- Mitsuyama, Y. (1984). Presenile dementia with motor neuron disease in Japan: Clinico-pathological review of 26 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, 47, 953–959.
- Mitsuyama, Y., & Takamiya, S. (1979). Presenile dementia with motor neuron disease in Japan: A new entity? *Archives of Neurology*, 36, 592–593.
- Neary, D., Snowden, J. S., Mann, D. M. A., Northen, B., Goulding, P. J., & Macdermott, N. (1990). Frontal lobe dementia and motor neuron disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 53, 23–32.
- Peavy, G. M., Herzog, A. G., Rubin, N. P., & Mesulam, M. M. (1992). Neuropsychological aspects of dementia of motor neurone disease: A report of two cases. *Neurology*, 42, 1004–1008.
- Pulvermüller, F., Härle, M., & Hummel, F. (2000). Neurophysiological distinction of verb categories. *Cognitive Neuroscience*, 11(12), 2789–2793.
- Pulvermüller, F., Lutzenberger, W., & Preiss, H. (1999). Nouns and verbs in the intact brain: Evidence from event-related potentials and high-frequency cortical responses. *Cerebral Cortex*, 9, 497–506.
- Rakowicz, Z., & Hodges, J. R. (1998). Dementia and aphasia in motor neurone disease: An under recognised association. *Journal of Neurology Neurosurgery and Psychiatry*, 65, 881–889.
- Rossor, M. N., Revesz, T., Lantos, P. L., & Warrington, E. K. (2000). Semantic dementia with ubiquitin-positive tau-negative inclusion bodies. *Brain*, 123, 267–276.
- Tsuchiya, K., Ozawa, E., Fukushima, J., Yasui, H., Kondo, H., Nakano, I., & Ikeda, K. (2000). Rapidly progressive aphasia and motor neuron disease: A clinical, radiological, and pathological study of an autopsy case with circumscribed lobar atrophy. *Acta Neuropathologica*, 99, 81–87.

- van Bogaert, L. (1925). Les troubles mentaux dans la sclérose latérale amyotrophique. *Encéphale*, 20–27.
- Vico, G. (1744). *Principi di scienza nuova*. Napoli: Stamperia Muziana.
- Warrington, E. K., & James, M. (1991). *The visual object and space perception battery*. Bury, St. Edmunds: Thames Valley Test Company.
- Wilkstrom, J., Paetau, A., Palo, J., Sulkava, R., & Haltia, M. (1982). Classic amyotrophic lateral sclerosis with dementia. *Archives of Neurology*, 39, 681–683.
- Ziegler, L. H. (1930). Psychotic and emotional phenomena associated with amyotrophic lateral sclerosis. *Archives of Neurology and Psychiatry, Chicago*, 24, 930–936.