Motor Neuron dysfunction in frontotemporal dementia

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Frontotemporal dementia and motor neuron disease share clinical, genetic and pathological characteristics. Motor neuron disease develops in a proportion of patients with frontotemporal dementia, but the incidence, severity and functional significance of motor system dysfunction in patients with frontotemporal dementia has not been determined. Neurophysiological biomarkers have been developed to document motor system dysfunction including: short-interval intracortical inhibition, a marker of corticospinal motor neuron dysfunction and the neurophysiological index, a marker of lower motor neuron dysfunction. The present study performed detailed clinical and neurophysiological assessments on 108 participants including 40 consecutive patients with frontotemporal dementia, 42 age- and gender-matched patients with motor neuron disease and 26 control subjects. Of the 40 patients with frontotemporal dementia, 12.5% had concomitant motor neuron disease. A further 27.3% of the patients with frontotemporal dementia had clinical evidence of minor motor system dysfunction such as occasional fasciculations, mild wasting or weakness. Biomarkers of motor system function were abnormal in frontotemporal dementia. Average short-interval intracortical inhibition was reduced in frontotemporal dementia (4.3 ± 1.7%) compared with controls (9.1 ± 1.1%, P < 0.05). Short-interval intracortical inhibition was particularly reduced in the progressive non-fluent aphasia subgroup, but was normal in patients with behavioural variant frontotemporal dementia and semantic dementia. The neurophysiological index was reduced in frontotemporal dementia (1.1) compared with controls (1.9, P < 0.001), indicating a degree of lower motor neuron dysfunction, although remained relatively preserved when compared with motor neuron disease (0.7, P < 0.05). Motor system dysfunction in frontotemporal dementia may result from pathological involvement of the primary motor cortex, with secondary degeneration of lower motor neurons in the brainstem and anterior horn of the spinal cord.

Keywords: frontotemporal dementia; motor neuron disease; transcranial magnetic stimulation; biomarkers

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Score – Revised; FTD = frontotemporal dementia; FUS = fused in sarcoma; MND = motor neuron disease; MRCSS = Medical Research Council Sum Score; PNFA = progressive non-fluent aphasia; TDP-43 = TAR DNA-binding protein 43
Introduction

The recognition of clinical, pathological and genetic overlaps between frontotemporal dementia (FTD) and motor neuron disease (MND) supports the view that FTD and MND form the extremes of a disease spectrum, with a predominance of cognitive symptoms at one end and motor dysfunction at the other (Clark and Forman, 2006; Neumann et al., 2006). Although evidence of such an overlap at pathological and genetic levels is now substantial, the frequency and severity of clinical and subclinical motor neuron dysfunction in FTD is unknown.

The neuropathology of FTD and MND remains complex, with many developments over recent years serving to reinforce shared characteristics (Clark and Forman, 2006; Mackenzie et al., 2010; Kiernan et al., 2011). Although FTD cases share a common pathological basis, abnormalities of three different proteins have been implicated and can be characterized immunohistochemically as follows: tau, TAR DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS) (Neumann et al., 2006, 2009; Mackenzie et al., 2010). While TDP-43-positive inclusions are the most common type in FTD, both TDP-43 and FUS are also detected in MND. Importantly, TDP-43 inclusions are present in almost all patients with sporadic MND (Sreedharan et al., 2008; Geser et al., 2009; Maekawa et al., 2009) and some familial cases (Mackenzie et al., 2010), while FUS-positive inclusions have been identified in other familial MND cases (Blair et al., 2010).

FTD and MND share an overlapping genetic basis. First, familial clusters of FTD and MND are reported. Within these clusters, one individual may develop FTD and another MND, or a third individual may develop FTD then MND. Several linkage studies of FTD-MND clusters have indicated a common locus on chromosome 9p13.2–21.3 (Le Ber et al., 2009; Laaksovirta et al., 2010; Boxer et al., 2011) but the responsible gene has not yet been identified. Furthermore, autosomal dominant inheritance of genes linked to FTD and MND has also been described. Mutations of TARDBP, which encodes TDP-43, recognized as a cause of familial MND, have been identified in cases of FTD-MND (Benajiba et al., 2009) and rarely in FTD (Borroni et al., 2009). In addition, mutations of the FUS gene have been demonstrated as a cause of familial MND (Blair et al., 2010) and have been identified in a minority of patients with FTD (Van Langenhove et al., 2010).

In further support of commonality, patients who present with MND may develop cognitive symptoms and some may satisfy the diagnostic criteria for the diagnosis of FTD (Lomen-Hoerth et al., 2003). Similarly, patients with FTD may subsequently develop MND (Lomen-Hoerth et al., 2002). Typically such patients present with mixed behavioural and aphasic features, but may also have prominent psychotic symptoms (Bak et al., 2001; Lillo et al., 2010). Whether MND or subclinical motor neuron dysfunction develops in all FTD subtypes has yet to be determined. Furthermore, the functional significance of subclinical motor system involvement remains unknown. As such, the present study aimed to identify clinical, functional and neurophysiological evidence of motor system dysfunction across a spectrum of consecutive patients with FTD. The incidence, pattern, severity and functional significance of motor system involvement in FTD was studied systematically and incorporated novel neurophysiological approaches including threshold tracking transcranial magnetic stimulation (Vucic and Kiernan, 2006; Vucic et al., 2008). In addition, these clinical parameters were compared across FTD subgroups to explore the relationship between phenotypes and motor system dysfunction.

Materials and methods

Patients

Consecutive patients with FTD referred to a specialist clinic (Frontier) at Neuroscience Research Australia were recruited using a cross-sectional study design. Patients were each assessed on a single occasion. Patients who developed prominent cognitive symptoms after the development of MND were excluded. Separately, patients with MND, age- and gender matched to the FTD group, were recruited from a specialized multi-disciplinary MND clinical service. Similar age and gender control subjects were recruited from a database of control subjects.

The diagnosis of FTD was made according to consensus criteria and further categorized into the recognized subtypes of FTD: behavioural variant FTD, progressive non-fluent aphasia (PNFA) and semantic dementia (Neary et al., 1998). The presence of frank MND in patients with FTD was also noted and for the purposes of secondary analysis such patients were designated FTD-MND. All patients underwent detailed clinical and neuropsychological evaluation using a standardized test battery and cerebral MRI. Behavioural changes were systematically explored, using caregiver questionnaires, and taken into account in the diagnostic formulation. Patients with PNFA all had either agrammatism or apraxia of speech, without clinical evidence of bulbar palsy. A family history of dementia or MND was systematically investigated in all patients with FTD. Patients with a family history suggestive of autosomal dominant inheritance were offered genetic testing for progranulin and microtubule-associated protein tau (MAPT) mutations. Patients with logopenic progressive aphasia were excluded (Gorno-Tempini et al., 2008, 2011). FTD phenocopy patients with behavioural symptoms, normal performance on formal neuropsychological testing and an absence of atrophy on MRI were excluded (Davies et al., 2006), as were patients with documented cervical radiculopathy, entrapment neuropathy or polynuropathy.

The diagnosis of MND was made in accordance with the El Escorial and Awaji criteria for MND (Brooks et al., 2000; de Carvalho et al., 2008). The Awaji criteria required the demonstration of clinical or electromyographic evidence of lower motor neuron dysfunction in regions with concomitant upper motor neuron signs. MND was diagnosed when combined lower and upper motor neuron dysfunction was identified in bulbar and spinal-innervated regions.

Neuropsychological and functional assessment

Cognitive screening of patients with FTD was completed using the Addenbrooke’s Cognitive Examination–Revised (Mioshi et al., 2006). Staging was performed using the newly developed Frontotemporal Dementia Rating Scale, a carer questionnaire, which assesses patient function and behaviour (Mioshi et al., 2010).
Clinical motor assessment

Patients underwent a standardized clinical motor assessment by a single examiner (J.B.), blind to the clinical classification of FTD subtype and the neuropsychological test results. In addition to the presence or absence of fasciculations and wasting, separate four point scales (0–3) were developed to determine the severity and distribution of these signs in multiple bulbar and limb regions (Supplementary Table 1). The scales were defined prior to the commencement of the study and, after piloting and refinement, were applied universally by a single examiner (J.B.). Individual grades were added to produce a ‘wasting’ and ‘fasciculation’ score for each patient with FTD. By definition, the normal value for each score was 0. Any degree of wasting or fasciculations (i.e. a wasting or fasciculation score >0) in the FTD cohort was regarded as clinically significant.

Limb power was assessed and graded according to the Medical Research Council grading system and added to calculate the Medical Research Council Sum Score (MRCSS) for each patient (Kleyweg et al., 1988). The MRCSS yields a total score of 60 in normal subjects. In order to document weakness of intrinsic hand muscles, which may be disproportionately affected in amyotrophic lateral sclerosis (Kuwabara et al., 2008), the MRCSS was modified to include finger flexion, extension and abduction grades, as well as great toe extensor grades, on both sides. The modified MRCSS, therefore, yielded a total of 100 in normal subjects. Any degree of limb weakness (i.e. a MRCSS score of <60 or modified MRCSS score <100) in the FTD cohort was regarded as clinically significant. Hyper-reflexia, defined as deep tendon reflexes elicited with minimal stimulus, or by pathological spread of reflexes, was noted in each patient.

Motor functional status was assessed using the Amyotrophic Lateral Sclerosis Functional Rating Score-Revised (ALSFRS-R) (Cedarbaum et al., 1999). ALSFRS-R items were also grouped into subcategories: bulbar, fine motor, gross motor and respiratory, each scored out of 12 points. The maximum ALSFRS-R total was 48 points with a greater reduction in the ALSFRS-R total indicating greater motor disability.

Transcranial magnetic stimulation

Transcranial magnetic stimulation was performed according to the paired pulse threshold tracking protocol (Vucic and Kiernan, 2006; Vucic et al., 2008). Magnetic stimulation of the motor cortex was delivered using a 90-mm circular coil placed on the patients scalp. The coil position was adjusted until a stable motor-evoked potential was recorded from the abductor pollicis brevis muscle of the hand at rest. Magnetic stimuli were generated by two magnetic stimulators connected via a BiStim (Magstim Co.), which allowed paired stimuli to be delivered through a single coil.

The resting motor threshold, defined as the single stimulus intensity required to achieve and maintain a target motor-evoked potential of 0.2 mV, was established. Impulses were then delivered in pairs; a sub-conditioning impulse followed by a test stimulus. The sub-conditioning stimulus intensity was fixed at 70% of resting motor threshold. The test stimulus intensity was varied to achieve the target motor-evoked potential of 0.2 mV and the difference between the test stimulus intensity and resting motor threshold was recorded and expressed as a percentage of resting motor threshold (Fisher et al., 2002; Vucic and Kiernan, 2006). The interval between the stimuli, or the interstimulus interval, was varied as the protocol proceeded.

Short-interval intracortical inhibition was defined as the percentage increase in test stimulus intensity required to achieve the target motor-evoked potential of 0.2 mV at interstimulus intervals of 1–7 ms (Vucic and Kiernan, 2006). Average short-interval intracortical inhibition was calculated as the mean of short-interval intracortical inhibition values recorded at each interstimulus interval from 1 to 7 ms. The motor responses were amplified and filtered (3 Hz–3 kHz) using a GRASS ICP511 AC amplifier (Grass-Telefactor, Astro-Med Inc.) and sampled at 10 kHz using a 12-bit data acquisition card (National Instruments PCI-MIO-16E-4). Data acquisition and stimulation delivery were controlled by QTRACS software (Institute of Neurology, Queen Square).

Following the paired-pulse threshold tracking protocol, the maximum motor-evoked potential amplitude and minimum motor-evoked potential onset latency were recorded after three single stimuli at 150% resting motor threshold intensity. In addition to measurement of raw motor-evoked potential amplitudes, the ratio of the motor-evoked potential amplitude to the compound motor action potential amplitudes was calculated and expressed as a percentage. Central motor conduction time was calculated according to the F-wave method (Robinson et al., 1988; Claus, 1990) as:

\[
\text{Central motor conduction time} = (\text{motor evoked potential latency}) - (F-\text{wave latency} + \text{distal motor latency} - 1)/2
\]

Maximal cortical silent period, defined as the maximum duration of electrical silence following a motor-evoked potential that interfered with ongoing EMG activity, was recorded while patients performed weak voluntary contraction. Three single stimuli at 150% resting motor threshold intensity were administered with resultant silent period measurements averaged to determine the maximum cortical silent period. The duration of the silent period was measured from motor-evoked potential onset to the return of EMG activity (Cantello et al., 1992).

Patients with FTD included in the study were not administered centrally active agents at the time of transcranial magnetic stimulation and patients with MND were studied prior to the initiation of riluzole. In addition, all patients were studied while at rest and encouraged to remain relaxed. If the study data quality was degraded by patient movement the protocol was recommenced, and the initial data discarded.

Peripheral studies

The distal motor latency (recorded in milliseconds), maximal compound motor action potential amplitude (recorded in millivolts), F-wave frequency and minimum F-wave latency (recorded in milliseconds) were all recorded from the abductor pollicis brevis muscle in each patient following electrical stimulation of the median nerve at the wrist. F-waves were recorded following 20 or more supramaximal anti-dromic stimulations of the median nerve. F-wave frequency was calculated as the number of recorded F-waves divided by the total number of stimulations.

The neurophysiological index was calculated for each patient. The neurophysiological index is a composite of the compound motor action potential amplitude, the F-wave frequency and the distal motor latency, which are abnormal in the context of lower motor neuron dysfunction (Mills and Nithi, 1998). The neurophysiological index is reduced as lower motor neuron dysfunction progresses (de Carvalho et al., 2003) and was calculated as:

\[
\text{Neurophysiological index} = (\text{compound motor action potential amplitude}/\text{distal motor latency}) \times (F-\text{wave frequency})
\]

Electromyography was used to confirm the diagnosis of MND in patients with significant symptoms and signs of motor system dysfunction.
Statistical methods

Statistical analysis was performed by a single author (J.B.) and carried out using the Statistical Package for Social Sciences (version 17.0, SPSS Inc). Paired continuous data were analysed with independent t-tests, when normally distributed, or the Mann–Whitney test when non-normally distributed. Group comparisons were performed using a one-way ANOVA when normally distributed or the Kruskal–Wallis test when non-normally distributed. Categorical data were analysed using the chi-square test. P < 0.05 were regarded as statistically significant.

Comparison of clinical parameters was first made between patients with FTD—including those with concomitant MND—and patients with MND. Patients with FTD were then divided into subgroups (behavioural variant FTD, PNFA and semantic dementia) and these were compared. Similarly, neuropsychological parameters were first compared between patients with FTD as a whole, control subjects and patients with MND, followed by a comparison of FTD subgroups. Finally, patients who developed MND after the onset of cognitive symptoms (referred to as FTD-MND) were compared with other patients with FTD.

Results

Patient demographics

A total of 82 patients and 26 controls underwent investigation; 40 patients with FTD and 42 patients with MND (Table 1). Patients with FTD were sub-categorized as behavioural variant FTD (n = 18), PNFA (n = 12) and semantic dementia (n = 10). Five patients in the FTD cohort were found to have frank MND and met the El Escorial and Awaji criteria for MND (Brooks et al., 2000; de Carvalho et al., 2008); these were designated as FTD-MND cases. Of the five, three had behavioural variant FTD and two had PNFA; one patient with PNFA had limb-onset MND and the other bulbar-onset MND. Of the 40 patients with FTD, 13 had a family history of dementia or MND suggestive of autosomal dominant inheritance and 11 underwent genetic testing. No known pathogenic mutations of progranulin or MAPT were identified.

In the MND cohort, limb-onset disease accounted for 30 patients and bulbar-onset disease for 12 patients. Overall, patients with FTD had significantly longer mean symptom duration when compared with MND (FTD: 51.2 ± 31.7 months; MND: 21.5 ± 14.9 months; P < 0.001). There were no differences in symptom duration between FTD subgroups, even when with FTD-MND patients were included.

Cognitive profile

The FTD cohort was representative of patients diagnosed with the spectrum of FTD syndromes in a specialist centre, with behavioural variant FTD being the single largest subgroup. Patients with primary progressive aphasia were split equally between PNFA and semantic dementia. Overall, the level of cognitive impairment was moderate with a mean Addenbrooke’s Cognitive Examination–Revised total score of 65.2 points (normal > 88). As shown in Table 2, patients with semantic dementia performed poorly on the Addenbrooke’s Cognitive Examination–Revised, with a reduced total score compared to other FTD subgroups, driven by poor performance on memory and language subscores. Scores on the Frontotemporal Dementia Rating Scale showed a greater proportion of mild or very mild functional impairment in the PNFA group compared to the behavioural variant FTD and semantic dementia subgroups.

Patients with frontotemporal dementia-motor neuron disease

There were no significant differences in the level of cognitive impairment between the five patients with FTD-MND and other patients with FTD. On average, patients with FTD with MND scored slightly lower on the Addenbrooke’s Cognitive Examination–Revised than other patients with FTD (FTD-MND: 55.2 ± 23.1; other FTD: 66.7 ± 16.7; P = 0.18), but this difference was not significant. There were no significant differences in Addenbrooke’s Cognitive Examination–Revised subscores between the two patient groups. Cognitive functional impairment, assessed using the Frontotemporal Dementia Rating Scale, was similar in both groups; 60% of the patients with FTD-MND had moderate to severe functional impairment, compared with 62.9% of other patients with FTD.

Clinical evidence of motor dysfunction

The presence of muscle wasting, defined as a wasting score > 0, was detected in 30% of the patients with FTD, compared with 90% of the patients with MND (P < 0.001; Table 3). The degree of wasting in FTD was minor compared with MND, as reflected by differences in the mean wasting score. When present, wasting was most commonly identified in the distal upper limb muscles, in both FTD and MND cohorts.

Table 1 Patient demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>FTD</th>
<th>MND</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>40</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>31 (77.5)</td>
<td>32 (76.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>63.8 ± 0.7</td>
<td>63.8 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>47–82</td>
<td>47–78</td>
<td>NS</td>
</tr>
<tr>
<td>Symptom duration (years ± SD)</td>
<td>51.2 ± 31.7</td>
<td>21.5 ± 14.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Patients with MND were age- and gender matched to the FTD cohort. The FTD group had significantly longer symptom duration than the MND group. NS = non-significant.
Fasciculations were identified in 17.5% of the patients with FTD compared with 90% of the patients with MND ($P < 0.001$). The fasciculation score was significantly lower in FTD compared with MND ($P < 0.001$), reflecting infrequent fasciculations in the FTD group. Consistent with the pattern of wasting, fasciculations were located predominantly in the distal upper limbs in FTD and MND. The majority of the patients with FTD had normal limb power, as reflected by the mean MRCSS and modified MRCSS scores,
which were preserved in the FTD group compared with the MND group ($P < 0.001$). In contrast, limb weakness reflected by a reduced modified MRCSS score was detected in 80% of the patients with MND, with an isolated bulbar palsy phenotype in the other 20% of the patients with MND (Burrell et al., 2011). Corresponding to the pattern of limb wasting and fasciculations, the most common site of weakness in both groups was the distal upper limbs. Hyper-reflexia was common in both FTD and patients with MND.

Patients with FTD had little or no motor functional impairment when scored using the ALSFRS-R, and scored significantly better than patients with MND (FTD: $46.2 \pm 2.2$; MND: $40.3 \pm 5.3$; $P < 0.001$). As may be expected, patients with MND scored lower on the bulbar and gross motor ALSFRS-R subscores. There was also a trend towards reduced fine motor and respiratory ALSFRS-R subscores in MND compared with FTD.

The patients with FTD with frank MND (i.e. the FTD-MND group) accounted for a significant proportion of those with clinically detected motor system dysfunction in the FTD group. Even after excluding the five patients with FTD-MND, clinical evidence of motor system dysfunction (i.e. some degree of limb wasting, fasciculations or weakness) was identified in 27.3% of the remaining patients with FTD compared with 95% of the patients with MND ($P < 0.001$). Importantly, the degree of clinically detected motor system dysfunction was mild and not sufficient to satisfy a diagnosis of MND.

**Comparison of frontotemporal dementia subgroups**

Mild wasting, weakness or fasciculations were identified in a proportion of all FTD subgroup patients (Table 4). For example, mild wasting was detected in up to 30% of behavioural variant FTD, PNFA and semantic dementia patients. Furthermore, occasional fasciculations were identified in a minority of behavioural variant FTD and patients with PNFA. Of note, none of the 10 patients with semantic dementia had fasciculations. In addition, mild weakness, defined as an MRCSS total < 60, was identified in a minority of behavioural variant FTD and patients with PNFA, but not in patients with semantic dementia. When present, weakness affected the distal upper limbs in all patient groups. Hyper-reflexia was common in all patient groups.

Mild motor functional impairment, reflected in a slightly reduced ALSFRS-R total, was detected in the PNFA group when compared with other subgroups. In contrast, patients with behavioural variant FTD or semantic dementia had little if any motor functional impairment. Patients with PNFA also had reduced ALSFRS-R bulbar and fine motor subscores compared with behavioural variant FTD and semantic dementia.

### Table 4 Clinical characteristics of FTD subgroups

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Behavioural variant FTD</th>
<th>PNFA</th>
<th>Semantic dementia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of motor dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness, wasting or fasciculations (% of patients)</td>
<td>7 (38.9)</td>
<td>4 (33.3)</td>
<td>2 (20.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Wasting</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Wasting score</td>
<td>$0.4 \pm 0.7$</td>
<td>$2.0 \pm 4.0$</td>
<td>$0.3 \pm 0.7$</td>
<td>NS</td>
</tr>
<tr>
<td>Wasting (% of patients)</td>
<td>4 (22.2)</td>
<td>4 (33.3)</td>
<td>2 (20.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Distal upper limb wasting (% of patients)</td>
<td>3 (16.7)</td>
<td>4 (33.3)</td>
<td>2 (20.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Fasciculations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasciculation score</td>
<td>$1.7 \pm 4.7$</td>
<td>$1.7 \pm 4.7$</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Fasciculations (% of patients)</td>
<td>3 (16.7)</td>
<td>2 (16.7)</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hyper-reflexia</td>
<td></td>
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<tr>
<td>Hyper-reflexia (% of patients)</td>
<td>12 (75.0)</td>
<td>10 (83.3)</td>
<td>4 (40.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRCSS total (/60)</td>
<td>$59.8 \pm 0.5$</td>
<td>$59.1 \pm 1.8$</td>
<td>60.0</td>
<td>NS</td>
</tr>
<tr>
<td>Modified MRCSS total (/100)</td>
<td>$99.6 \pm 1.1$</td>
<td>$98.2 \pm 3.5$</td>
<td>99.9</td>
<td>NS</td>
</tr>
<tr>
<td>Weakness—MRCSS (% of patients)</td>
<td>2 (11.1)</td>
<td>3 (25.0)</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Weakness—modified MRCSS (% of patients)</td>
<td>3 (16.7)</td>
<td>3 (25.0)</td>
<td>1 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Distal upper limb weakness (% of patients)</td>
<td>2 (11.1)</td>
<td>3 (25.0)</td>
<td>1 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Motor functional impairment</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ALSFRS-R total</td>
<td>$47.2 \pm 1.2$</td>
<td>$43.9 \pm 2.4$</td>
<td>47.5</td>
<td>&lt;0.001 $^{a,b}$</td>
</tr>
<tr>
<td>ALSFRS-R bulbar</td>
<td>$11.6 \pm 0.6$</td>
<td>$9.3 \pm 1.7$</td>
<td>11.7</td>
<td>&lt;0.001 $^{a,b}$</td>
</tr>
<tr>
<td>ALSFRS-R fine motor</td>
<td>$11.8 \pm 0.5$</td>
<td>$11.2 \pm 0.8$</td>
<td>11.9</td>
<td>&lt;0.05 $^{a,b}$</td>
</tr>
<tr>
<td>ALSFRS-R gross motor</td>
<td>$11.8 \pm 0.4$</td>
<td>$11.6 \pm 0.8$</td>
<td>11.9</td>
<td>NS</td>
</tr>
<tr>
<td>ALSFRS-R respiratory</td>
<td>$11.9 \pm 0.3$</td>
<td>$11.8 \pm 0.4$</td>
<td>12.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Clinical evidence of motor system dysfunction was spread across all FTD subgroups, although patients with PNFA had greater motor disability as assessed by the ALSFRS-R.  

a PNFA compared with behavioural variant FTD ($P < 0.05$).  
b PNFA compared to semantic dementia ($P < 0.05$).  
NS = non-significant.
Patients with frontotemporal dementia-motor neuron disease

As might be expected, patients with FTD-MND had more clinical evidence of motor system dysfunction than other patients with FTD. Patients with FTD-MND had a higher frequency of fasciculations (FTD-MND 60%; other FTD 6.1%, P < 0.05) and the fasciculation score was increased when compared with other patients with FTD (FTD-MND: 8.2 ± 8.6; other FTD: 0.2 ± 0.8; P < 0.05). In addition, 60% of the patients with FTD-MND had clinically detectable limb weakness compared with only 6.1% of other patients with FTD (P < 0.05). Despite these findings, motor functional impairment was similar in both groups and the average ALSFRS-R total was similar in patients with FTD-MND compared with other patients with FTD (FTD-MND: 45.2 ± 2.1; other FTD: 46.4 ± 2.2; P = 0.11).

Central studies

Cortical excitability, as assessed using threshold tracking transcranial magnetic stimulation, was abnormal in FTD when compared with controls, confirming motor system dysfunction, although the abnormalities were not as dramatic as in the MND cohort (Table 5). Specifically, while resting motor threshold was not different between groups, central motor conduction time differed significantly (P < 0.01), with post hoc analysis revealing prolongation of central motor conduction time in the FTD group compared with controls and the MND group (i.e. FTD > controls = MND). In addition, intergroup analysis revealed a trend (P = 0.06) towards an increased motor-evoked potential amplitude when expressed as a percentage of the compound motor action potential amplitude in the FTD group compared with controls, which was similar to the MND group.

The most striking abnormality in the FTD cohort related to reduction in short-interval intracortical inhibition. The stimulus intensity required to achieve the target motor-evoked potential amplitude of 0.2 mV normally increases with the interstimulus interval, peaking at an interstimulus interval of 3 ms (Fig. 1A). In contrast, this increase in stimulus intensity was attenuated in the FTD group, indicating reduced short-interval intracortical inhibition compared with controls. Average short-interval intracortical inhibition (reflecting interstimulus intervals 1–7 ms) differed significantly (P < 0.05) between groups, and post hoc analyses revealed a significant decrease in average short-interval intracortical inhibition in FTD when compared with controls, similar to patients with MND (FTD: 4.3 ± 10.0%; controls: 9.1 ± 5.5%; MND: 3.2 ± 9.4%; P < 0.05; Fig. 1B). Consistent with these results, peak short-interval intracortical inhibition at an interstimulus interval of 3 ms differed significantly between groups, with reduced peak short-interval intracortical inhibition in the FTD group when compared with controls (FTD: 8.3 ± 13.3%; controls: 15.3 ± 9.5%; P < 0.05), although not as marked as observed in the MND group (6.1 ± 11.6%). There was an intergroup difference in maximum cortical silent period; post hoc tests demonstrated a trend (P = 0.129) for reduced maximum cortical silent period in patients with FTD compared with controls, which was significantly reduced in MND (FTD: 199.4 ± 42.5 ms; controls: 243.4 ± 159.3 ms; MND: 178.8 ± 52.7 ms; P < 0.05).

### Table 5 Neurophysiological evidence of motor system dysfunction in FTD (including patients with FTD-MND) compared with MND and controls

<table>
<thead>
<tr>
<th>Neurophysiological measure</th>
<th>FTD</th>
<th>MND</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>40</td>
<td>42</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Peripheral studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal motor latency (ms ± SD)</td>
<td>4.3 ± 1.1</td>
<td>4.5 ± 0.6</td>
<td>4.2 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Compound motor action potential (mV ± SD)</td>
<td>7.3 ± 3.6</td>
<td>4.7 ± 2.4</td>
<td>8.3 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neurophysiological index (± SD)</td>
<td>1.1 ± 0.9</td>
<td>0.7 ± 0.6</td>
<td>1.9 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting motor threshold (% ± SD)</td>
<td>60.6 ± 12.4</td>
<td>59.4 ± 10.8</td>
<td>61.8 ± 9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Motor-evoked potential amplitude (mV ± SD)</td>
<td>2.2 ± 1.5</td>
<td>1.7 ± 0.7</td>
<td>2.3 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Motor-evoked potential ratio % (% CMAP ± SD)</td>
<td>36.5 ± 28.3</td>
<td>43.8 ± 26.4</td>
<td>26.7 ± 13.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Motor-evoked potential latency (ms ± SD)</td>
<td>25.0 ± 2.6</td>
<td>24.7 ± 2.6</td>
<td>21.8 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central motor conduction time (ms ± SD)</td>
<td>8.2 ± 2.9</td>
<td>6.9 ± 2.4</td>
<td>5.9 ± 1.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Average SICI (± SD)</td>
<td>4.3 ± 10.0</td>
<td>3.2 ± 9.4</td>
<td>9.1 ± 5.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peak SICI (at interstimulus interval 3 ms, ± SD)</td>
<td>8.3 ± 13.3</td>
<td>6.1 ± 11.6</td>
<td>15.3 ± 9.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Average ICF (± SD)</td>
<td>−2.6 ± 7.2</td>
<td>−1.7 ± 6.3</td>
<td>−1.4 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum cortical silent period (ms ± SD)</td>
<td>199.4 ± 42.5</td>
<td>178.8 ± 52.7</td>
<td>243.4 ± 159.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

The compound motor action potential amplitude was normal in FTD, but reduced in MND compared with controls. However, the neurophysiological index was reduced in the FTD group compared with controls, but relatively preserved compared with the MND group. The central motor conduction time was prolonged in the FTD group compared with controls, but relatively preserved compared with the MND group. The average short-interval intracortical inhibition was reduced in FTD and MND compared with controls.

a FTD compared with controls (P < 0.05).
b FTD compared with MND (P < 0.05).
c MND compared with controls (P < 0.05).
CMAP = compound motor action potential; ICF = intracortical facilitation; SICI = short-interval intracortical inhibition.
Comparison of frontotemporal dementia subgroups

Evidence of corticospinal dysfunction was evident in all FTD subgroups, although the abnormalities were most marked in PNFA (Table 6). While there were no significant intergroup differences, average short-interval intracortical inhibition was reduced in the PNFA subgroup compared with controls (Fig. 2, P < 0.05). Similarly, there was no intergroup difference in peak short-interval intracortical inhibition when measured at an interstimulus interval of 3 ms, but there was a trend for reduced peak short-interval intracortical inhibition in PNFA compared with controls (P = 0.056). In addition, motor-evoked potential latency was prolonged in all FTD subgroups compared with controls (P < 0.001) and central motor conduction time was prolonged in behavioural variant FTD and semantic dementia (P < 0.05).

Although raw motor-evoked potential amplitudes were not significantly different between subgroups, there was a trend for an increased motor-evoked potential amplitude when expressed as a percentage of compound motor action potential amplitude in PNFA (P = 0.08), consistent with the finding of reduced short-interval intracortical inhibition. There was no significant difference in maximum cortical silent period across FTD subgroups.

Patients with frontotemporal dementia-motor neuron disease

Although there were no significant differences in transcranial magnetic stimulation parameters, there was a trend for reduced short-interval intracortical inhibition in the FTD-MND group compared with other patients with FTD (FTD-MND: 1.8 ± 4.5%; other FTD: 4.6 ± 10.6%; P = 0.26). Consistent with this finding, there was a trend for increased motor-evoked potential amplitude, when expressed as a percentage of compound motor action potential amplitude, in the FTD-MND group (FTD-MND: 44.7 ± 26.7%; 35.1 ± 28.8%; P = 0.34). In addition, there was a non-significant increase in central motor conduction time in the FTD-MND group compared with other patients with FTD (FTD-MND: 9.5 ± 5.1 ms; other FTD: 7.9 ± 2.4 ms; P = 0.78).

Peripheral studies

Neurophysiological investigations established evidence of lower motor neuron dysfunction in the FTD group when compared with controls, although these abnormalities were less severe than those observed in the MND cohort (Table 5). The compound motor action potential amplitude was preserved in the FTD group compared with controls, but reduced in the MND group (FTD: 7.3 ± 3.6 mV; controls: 8.3 ± 2.9 mV; MND: 4.7 ± 2.4 mV; P < 0.001). The distal motor latency did not differ between groups. Despite preservation of compound motor action potential amplitude and distal motor latency in the FTD group, the neurophysiological index was reduced in the FTD group compared with controls, but not as dramatically as in the MND group (FTD: 1.1 ± 0.9; controls: 1.9 ± 0.8; MND: 0.7 ± 0.6; P < 0.001; Fig. 3A). Taken together, these results indicate that lower motor neuron dysfunction was detectable in the FTD group compared with controls, albeit less severe than in the MND group.

Comparison of frontotemporal dementia subgroups

Neurophysiological evidence of lower motor neuron dysfunction was identified in all FTD subgroups, with the exception of semantic dementia (Table 6). Consistent with the transcranial magnetic stimulation findings, these abnormalities were most marked in the PNFA subgroup. Although the compound motor action potential amplitude and distal motor latency did not differ between FTD subgroups, the neurophysiological index was significantly reduced in the PNFA and behavioural variant FTD subgroups compared with controls, indicating lower motor neuron dysfunction (Fig. 3B).

Patients with frontotemporal dementia-motor neuron disease

As expected, lower motor neuron dysfunction was more prominent in the FTD-MND group compared with other patients with
Discussion

The present study has identified substantial motor system dysfunction in a large cohort of patients with FTD. Although clinically detectable motor system involvement was relatively minor in patients with FTD, significant corticospinal and lower motor neuron dysfunction was detected across most FTD subtypes using specialized neurophysiological biomarkers, establishing subclinical motor system dysfunction in FTD. These findings support the concept of an FTD-MND clinical-pathological continuum. Despite similar symptom durations across the spectrum of patients with FTD, biomarkers of motor system dysfunction were most abnormal in patients who presented with PNFA, and to a lesser degree behavioural variant FTD, compared with semantic dementia.

The prevalence, pattern and functional relevance of clinically detectable motor system dysfunction in patients with FTD have not been studied in any detail. One previous study of 36 patients with FTD identified definite MND in 14% and possible MND in 36% of the cases; however, the pattern and severity of motor system involvement was not reported (Lomen-Hoerth et al., 2002). A further retrospective report of pathologically confirmed FTD-MND identified clinical evidence of motor neuron dysfunction in 59% of cases; however, detailed clinical information was not presented (Josephs et al., 2006a). Earlier single case reports of FTD-MND reported prominent intrinsic hand muscle wasting and weakness, often in association with progressive bulbar dysfunction (Mitsuyama and Takamiya, 1979; Neary et al., 1990).

In the present study, 12.5% of patients in a FTD cohort had MND and a greater proportion had clinical evidence of motor system dysfunction, which was mild and insufficient to satisfy the diagnostic criteria for MND. In keeping with the relatively minor weakness and other clinical signs, the degree of functional impairment, as measured by functional rating scales, was mild in FTD, although fine motor skills were slightly impaired in patients with PNFA. When present, evidence of lower motor neuron dysfunction such as wasting, weakness and fasciculations, often involved the distal upper limbs. Whether subtle clinical evidence

FTD. There were no significant differences in distal motor latency or compound motor action potential amplitude, but there was a trend for reduced neurophysiological index in the FTD-MND group compared with other patients with FTD (FTD-MND: 0.6 ± 0.6; other FTD: 1.2 ± 1.0; P = 0.12).

### Table 6 Neurophysiological evidence of motor system dysfunction in FTD subgroups

<table>
<thead>
<tr>
<th>Neurophysiological measure</th>
<th>Behavioural variant FTD</th>
<th>PNFA</th>
<th>Semantic dementia</th>
<th>Control</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>18</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal motor latency (ms)</td>
<td>4.2 ± 0.8</td>
<td>4.8 ± 1.5</td>
<td>4.1 ± 0.8</td>
<td>4.2 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Compound motor action potential (mV)</td>
<td>7.1 ± 3.4</td>
<td>6.8 ± 3.9</td>
<td>8.5 ± 3.6</td>
<td>8.3 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Neurophysiological index</td>
<td>1.1 ± 1.0</td>
<td>0.9 ± 0.7</td>
<td>1.4 ± 1.1</td>
<td>1.9 ± 0.8</td>
<td>&lt;0.05ab</td>
</tr>
<tr>
<td>Central studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting motor threshold (%)</td>
<td>60.4 ± 13.1</td>
<td>61.0 ± 15.8</td>
<td>60.1 ± 5.7</td>
<td>61.8 ± 9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Motor-evoked potential amplitude (mV)</td>
<td>2.1 ± 1.5</td>
<td>2.9 ± 1.8</td>
<td>1.5 ± 0.6</td>
<td>2.3 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Motor-evoked potential amplitude (% CMAP)</td>
<td>35.1 ± 28.1</td>
<td>49.8 ± 31.6</td>
<td>20.8 ± 14.5</td>
<td>26.7 ± 13.1</td>
<td>NS</td>
</tr>
<tr>
<td>Motor-evoked potential latency (ms)</td>
<td>25.9 ± 3.3</td>
<td>23.9 ± 1.6</td>
<td>25.1 ± 2.0</td>
<td>21.8 ± 2.2</td>
<td>&lt;0.001abc</td>
</tr>
<tr>
<td>Central motor conduction time (ms)</td>
<td>9.3 ± 3.4</td>
<td>6.6 ± 2.6</td>
<td>8.2 ± 1.0</td>
<td>5.9 ± 1.9</td>
<td>&lt;0.05abc</td>
</tr>
<tr>
<td>Average SICI (%)</td>
<td>6.2 ± 8.3</td>
<td>0.5 ± 12.4</td>
<td>6.1 ± 8.6</td>
<td>9.1 ± 5.5</td>
<td>NS</td>
</tr>
<tr>
<td>Peak SICI (%)</td>
<td>10.3 ± 11.8</td>
<td>4.0 ± 15.4</td>
<td>10.7 ± 12.6</td>
<td>15.3 ± 9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Average ICF (%)</td>
<td>−2.2 ± 4.8</td>
<td>−5.3 ± 9.9</td>
<td>0.5 ± 5.2</td>
<td>−1.4 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Max cortical silent period (ms)</td>
<td>206.9 ± 33.7</td>
<td>186.7 ± 56.3</td>
<td>203.8 ± 34.4</td>
<td>243.4 ± 159.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

The neurophysiological index was reduced in behavioural variant FTD and PNFA compared with controls. The motor-evoked potential latency was prolonged in all FTD subgroups compared with controls, and the central motor conduction time was prolonged in behavioural variant FTD and semantic dementia. Although there was no significant intergroup difference, average short-interval intracortical inhibition was reduced in PNFA compared with controls (P = 0.05).

The prevalence, pattern and functional relevance of clinically detectable motor system dysfunction in patients with FTD have not been studied in any detail. One previous study of 36 patients with FTD identified definite MND in 14% and possible MND in 36% of the cases; however, the pattern and severity of motor system involvement was not reported (Lomen-Hoerth et al., 2002). A further retrospective report of pathologically confirmed FTD-MND identified clinical evidence of motor neuron dysfunction in 59% of cases; however, detailed clinical information was not presented (Josephs et al., 2006a). Earlier single case reports of FTD-MND reported prominent intrinsic hand muscle wasting and weakness, often in association with progressive bulbar dysfunction (Mitsuyama and Takamiya, 1979; Neary et al., 1990).

In the present study, 12.5% of patients in a FTD cohort had MND and a greater proportion had clinical evidence of motor system dysfunction, which was mild and insufficient to satisfy the diagnostic criteria for MND. In keeping with the relatively minor weakness and other clinical signs, the degree of functional impairment, as measured by functional rating scales, was mild in FTD, although fine motor skills were slightly impaired in patients with PNFA. When present, evidence of lower motor neuron dysfunction such as wasting, weakness and fasciculations, often involved the distal upper limbs. Whether subtle clinical evidence...
of motor system dysfunction represented the onset of secondary MND in the present series remains unknown.

Biomarkers of motor system dysfunction

The most striking finding was the dramatic reduction of short-interval intracortical inhibition in patients with PNFA indicating dysfunction of the motor pathways. In contrast, short-interval intracortical inhibition was relatively preserved in the behavioural variant FTD and semantic dementia subgroups. These findings may initially appear at odds with the existing literature, although prior studies have reported relatively small groups. For example, one previous study of eight patients with FTD reported normal short-interval intracortical inhibition; however, FTD subtypes were not taken into consideration (Pierantozzi et al., 2004). Another study did not identify reduced short-interval intracortical inhibition in 10 patients with behavioural variant FTD and three patients with PNFA (Alberici et al., 2008). Interestingly, reduced short-interval intracortical inhibition has been reported in corticobasal syndrome (Frasson et al., 2003; Alberici et al., 2008), a neurodegenerative disorder that shares clinical and pathological similarities with PNFA (Josephs et al., 2006b, c). On longitudinal follow-up, many patients with corticobasal syndrome develop non-fluent aphasia, while those with a PNFA presentation frequently become apraxic (Kertesz and McMonagle, 2010).

While some of the patients with PNFA in the present series had mild, symmetrical apraxia, none had other clinical features such as myoclonus, alien limb phenomenon, eye movement abnormalities or early falls, suggestive of either corticobasal syndrome or progressive supranuclear palsy. Nonetheless, the observation of reduced short-interval intracortical inhibition in PNFA in the present series is further consistent with an overlap between corticobasal syndrome and PNFA.

Apart from reduced short-interval intracortical inhibition, motor-evoked potential latency and central motor conduction times were prolonged in patients with FTD in the present series. Central motor conduction time represents an estimate of the conduction time from the motor cortex to the spinal or bulbar neurons (Chen et al., 2008) and modest prolongation of central motor conduction time is recognized in MND (Eisen et al., 1990; Miscio et al., 1999; Floyd et al., 2009). Prolongation of the central motor conduction time, presumably due to axonal loss, is consistent with degeneration of corticospinal tracts, a recognized pathological feature of frontotemporal lobar degeneration, particularly in the context of FTD-MND (Cairns et al., 2007). Furthermore, prolonged central motor conduction time has been correlated in patients with MND with upper motor neuron dysfunction and motor disability, as well as abnormalities of corticospinal tracts detected using diffusion tensor MRI (Iwata et al., 2008). Although not previously reported in FTD, prolonged central motor conduction time in the present study most likely represents subclinical corticospinal dysfunction. Consistent with this interpretation, hyper-reflexia was as frequent in the FTD group as in the MND group.

Although clinical evidence of lower motor neuron dysfunction was infrequent in FTD, with the exception of semantic dementia, all FTD subtypes had abnormalities of lower motor neuron biomarkers, which have not previously been investigated in FTD. Significant reductions in the neurophysiological index, which is a sensitive marker of progressive lower motor neuron degeneration in MND (de Carvalho and Swash, 2010), were detected in PNFA and behavioural variant FTD, but the neurophysiological index was normal in semantic dementia. The development of lower motor neuron dysfunction may be secondary to upper motor neuron degeneration. According to the ‘dying forward hypothesis’, at least as it relates to MND pathogenesis, the cortical motor neuron is the initial target in MND, with secondary degeneration of lower motor neurons (Eisen et al., 1992). In support of this hypothesis, upper motor neuron dysfunction has been demonstrated early in the course of MND (Vucic and Kiernan, 2006; Vucic et al., 2008). Whether similar processes, initiated by frontal cortical pathology in FTD, result in downstream lower motor neuron degeneration remains to be established.

Patients with FTD found to have frank MND had greater clinical and neurophysiological evidence of motor system dysfunction. Although the number of patients with FTD-MND in the present cohort was limited, clinically detectable fasciculations and weakness were significantly more common in patients with FTD-MND than other patients with FTD. In addition, there was a trend for biomarkers of upper motor neuron and lower motor neuron dysfunction to be abnormal in FTD-MND compared with other patients with FTD. Whether abnormalities of neurophysiological
Is motor system dysfunction related to underlying pathology?

Motor system dysfunction may reflect the pattern of cortical atrophy of different FTD phenotypes rather than the nature of the underlying proteinopathy. Specifically, involvement of the primary motor cortex, located at the precentral gyrus (Yoursy et al., 1997), most likely underpins the changes in upper motor neuron function detected in the present series. Atrophy of this region has been reported in FTD by MRI voxel-based morphometry. In PNFA, the main locus of pathology focuses on the inferior frontal region (Broca’s area) and the anterior insula (Nestor et al., 2003; Rohrer et al., 2009). Atrophy of the left precentral gyrus has also been demonstrated (Nestor et al., 2003; Gorno-Tempini et al., 2004), yet the pathology underlying the syndrome is heterogeneous (Hodges et al., 2004; Seelaar et al., 2011). In contrast, semantic dementia is characterized by asymmetrical anterior temporal lobe atrophy with sparing of lateral frontal regions even at post-mortem (Gorno-Tempini et al., 2004; Davies et al., 2005; Rohrer et al., 2009), which may explain the finding of preserved short-interval intracortical inhibition in patients with semantic dementia in the present series. Bilateral atrophy of the precentral gyrus, associated with widespread frontal and temporal atrophy, has been demonstrated in MND, and a similar pattern of atrophy has been demonstrated in FTD-MND (Chang et al., 2005; Grosskreutz et al., 2006; Mezzapesa et al., 2007).

In contrast, motor system dysfunction may not be specifically associated with the underlying proteinopathy in FTD. TDP-43-positive intraneuronal inclusions are identified in the majority of cases with sporadic MND and semantic dementia (Cairns et al., 2007; Snowden et al., 2007), but the pattern of inclusions differs between clinical phenotypes. Patients with FTD associated with MND show extensive neuronal cytoplasmic inclusions involving frontoinsular and medial frontal regions (Mackenzie, type 3), whereas those with semantic dementia show involvement of the temporal poles (Mackenzie, type 2) (Mackenzie et al., 2010). Moreover, mutations of the TARDBP gene are generally associated with clinically expressed MND, rather than semantic dementia, which is very rarely inherited. Consistent with these studies, a marked reduction in short-interval intracortical inhibition was identified in patients with MND, but not semantic dementia, from the present series. In addition, familial MND due to superoxide dismutase-1 mutations may develop detectable upper motor neuron dysfunction (Vucic et al., 2008), despite an absence of TDP-43-positive intraneuronal inclusions.

Patients with PNFA in the present series revealed evidence of upper motor neuron dysfunction, despite the association of PNFA with predominantly tau positive intraneuronal inclusion pathology (Llado et al., 2008). Clinico pathological studies of PNFA have shown considerable heterogeneity in terms of the underlying pathology, but these studies predated the identification of the logopenic variant, which appears to be associated with Alzheimer’s pathology (Gorno-Tempini et al., 2008, 2011). We excluded patients with logopenic progressive aphasia; therefore, the majority of our cases with PNFA are likely to have underlying tauopathy.

Clinical implications

The present study has established that 10–15% of the patients with FTD have MND that meets standard clinical criteria for diagnosis, and that there is subtle evidence of motor system dysfunction in a significant cohort of patients with FTD. This motor impairment in patients with FTD without coexisting MND is unlikely to have secondary impacts on functional ability and quality of life. It is possible that a proportion of patients with FTD with more subtle motor dysfunction would progress to meet criteria for MND if followed longitudinally. In addition, the finding of reduced short-interval intracortical inhibition in patients with PNFA from the present series suggests that motor system dysfunction relates to specific patterns of cortical atrophy, rather than underlying histopathology. Existing studies have not attempted to correlate short-interval intracortical inhibition with patterns of atrophy, and such analysis will be important. Whether mild symptoms and signs of motor system dysfunction predict prognosis, the future development of MND, or possibly prominent apraxia, remains unknown. It is unlikely that the differences in motor system involvement across subgroups, with more marked abnormalities in PNFA, reflect simply the stage of disease since the subgroups were fairly well matched for severity with, in fact, a higher proportion of more disabled patients in the behavioural variant FTD subgroup. Previous studies have demonstrated a poor prognosis for FTD-MND (Gräsbeck et al., 2003; Hodges et al., 2003), emphasizing the need for future longitudinal studies.

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Supplementary material

Supplementary material is available at Brain online.

References


