RESEARCH PAPER

Tracking the progression of social cognition in neurodegenerative disorders

Fiona Kumfor,¹,²,³ Muireann Irish,¹,³,⁴ Cristian Leyton,¹,³ Laurie Miller,³,⁵,⁶ Suncica Lah,³,⁶ Emma Devenney,¹,²,³ John R Hodges,¹,²,³ Olivier Piguet¹,²,³

ABSTRACT

Background and purpose Behavioural-variant frontotemporal dementia (bvFTD) and Alzheimer’s disease (AD) patients experience behavioural and emotion recognition alterations, yet understanding of how socioemotional processing is affected with disease progression is minimal. Additionally, evidence suggests that bvFTD patients with limited brain atrophy on neuroimaging at presentation (bvFTD-la) have a more benign course than those with marked atrophy (bvFTD-ma). Longitudinal investigation of these patients, however, is lacking.

Methods We investigated general cognition, emotion recognition and sarcasm detection in 20 bvFTD (8 with limited brain atrophy) and 17 AD patients longitudinally and used mixed models analyses to determine the level and rates of decline across groups over time.

Results At baseline, all patient groups performed worse than controls on general cognition and emotion recognition measures. The bvFTD-ma group showed significant impairment on the sarcasm detection task compared with controls. Longitudinally, an overall effect of time was present for general cognition (p<0.001); however, the rate of decline did not differ across groups. Trends for interactions between time and diagnosis were observed for both emotion recognition tasks (p=0.055; p=0.062), with the bvFTD-ma group declining more rapidly than AD or bvFTD-la groups. On the sarcasm detection task, the bvFTD-ma and AD patients declined, whereas bvFTD-la patients remained stable over time (p=0.002).

Conclusions Tasks of sarcasm detection represent a clinically useful tool to differentiate between bvFTD and AD at baseline. Furthermore, tasks of socioemotional functioning can track progression within bvFTD and identify bvFTD patients more likely to show a faster rate of decline.

INTRODUCTION

Behavioural-variant frontotemporal dementia (bvFTD) and Alzheimer’s disease (AD) are the two commonest dementia syndromes affecting individuals under 65 years of age.¹ Clinically, bvFTD patients present with changes in behaviour, personality and motivation,² and recent evidence has revealed bvFTD patients also experience severe emotion processing deficits, such as impaired emotion recognition.³⁻⁵ In contrast, AD patients show profound deficits in episodic memory, navigation and working memory,⁶ while emotion processing deficits are relatively mild.⁷ Differential diagnosis of these dementia syndromes remains difficult, particularly early in the disease process. In addition, increasing evidence demonstrates that episodic memory may also be impaired in bvFTD.⁸⁻¹⁰ Simple, reliable clinical tests that can delineate these dementia syndromes are therefore needed.

A second diagnostic issue is that all bvFTD patients do not progress at the same rate. A subset of bvFTD patients appear to show a benign course and do not deteriorate at the same speed as other bvFTD cases, despite meeting clinical diagnostic criteria for bvFTD at presentation.¹¹⁻¹³ Subsequent research has suggested that these cases, which have been referred to as phenocopy cases or non-progressors,¹¹⁻¹³ have limited atrophy and therefore are more likely to remain stable. In the absence of high-quality quantitative neuroimaging, however, identifying patients with this benign variant is challenging, despite having important implications for prognosis and planning of interventions.

Recent research suggests that tests assessing social cognition, rather than traditional cognitive domains, such as memory and language, may prove informative when attempting to distinguish bvFTD and AD.⁴⁻⁵⁻¹⁶⁻¹⁸ Emotion recognition is consistently more severely affected in bvFTD than in AD in the early stages of the disease.⁴⁻⁷⁻¹⁸ In addition, within bvFTD, patients with the benign course trend to show limited deficits in emotion processing, particularly on complex tasks, such as sarcasm detection.⁵

Few studies have examined changes in emotion processing in bvFTD and AD over time. Given the progressive nature of these disorders, increasing emotion processing deficits are likely, as brain regions supporting these abilities become involved. To date, only one study has examined emotion processing in bvFTD and AD longitudinally,¹⁹ although the results were somewhat surprising. Patients were assessed on a facial emotion recognition task at baseline and 3 years later. While AD patients showed a significant decline in facial emotion recognition at the 3-year follow-up, bvFTD patients appeared to improve. Performance in the bvFTD group, however, was highly variable, with three of the six patients showing a decline in performance over time. In addition, only 6 of the initial 18 bvFTD cases and 7 of 19 AD cases were available for testing after 3 years, which may have contributed to the unusual results. With a median survival rate of just 5 years following symptom onset in bvFTD,²⁰ a long duration between baseline and follow-up may have limited clinical relevance. It is also plausible that the three bvFTD cases that remained stable were those individuals with limited atrophy and therefore a more benign course.
of bvFTD; however, brain imaging was not available. To date, no studies have directly compared bvFTD patients with and without marked atrophy at baseline. Our understanding of how these patients’ socioemotional functioning fares over time is therefore limited.

This study aimed to (i) examine socioemotional functioning in bvFTD and AD patients longitudinally in order to identify group differences in the profile of emotion processing deficits and their rate of change across the disease course, and (ii) compare bvFTD patients with and without marked brain atrophy at baseline with AD patients in order to determine whether differential patterns of decline in socioemotional functioning tasks exist between these groups. Such an approach is crucial in understanding how individuals are affected by these neurodegenerative disorders and in determining the nature and rate of progression across dementia syndromes.

**MATERIALS AND METHODS**

**Participants**

In total, 20 bvFTD and 17 AD patients were recruited from FRONTIER, the frontotemporal dementia clinic at Neuroscience Research Australia, Sydney. All patients underwent clinical assessment by an experienced behavioural neurologist, neuropsychological assessment and structural MRI, and had been seen for follow-up at least once. Diagnosis was based on consensus between the behavioural neurologist, neuropsychologist and occupational therapist. All bvFTD and AD patients were diagnosed according to current clinical diagnostic criteria. AD patients met criteria for probable AD while bvFTD patients were included if they met criteria for probable or possible bvFTD. Disease severity was measured using the Frontotemporal Dementia Rating Scale (FRS). Of the 20 bvFTD cases, 17 were genetically screened for the C9ORF72 mutation and 4 were found to carry a mutation; 5 bvFTD cases with strong family history were screened for the MAPT mutation and none tested positive; and 17 bvFTD cases were screened for the progranulin mutation (GRN) with 1 positive case identified. Of the 17 AD cases, 14 were screened for C9ORF72 and 8 were screened for GRN and none tested positive for either mutation.

Twenty-four healthy controls were selected from the FRONTIER database and matched to patients according to age and education for baseline comparisons. Exclusion criteria for patients and controls included concurrent psychiatric disturbance, other types of dementia or neurological disease, history of substance abuse and/or use of medications with central nervous system effects. The South Eastern Sydney Local Health District and the University of New South Wales ethics committees approved the study. Participants or their person responsible provided informed consent in accordance with the Declaration of Helsinki. Participants volunteered their time and were reimbursed for travel costs. All patients were tested at least twice and, where possible, followed up annually. All data are included until the point of drop out. The outcome variables were obtained approximately annually.

**Classification of bvFTD patients**

Patients underwent a 3-Tesla T1 weighted MRI scan. Previously validated MRI visual rating scales based on coronal T1 images were used for the orbitofrontal cortex and anterior temporal lobe, as well as the hippocampus. Areas of atrophy were rated on a Likert scale ranging from 0 (no atrophy) to 4 (severe atrophy) by a rater (ED) blinded to dementia diagnosis after appropriate training on an independent data set. Inter-rater reliability on the training set was assessed using intraclass correlation coefficient and was found to be very high (Cronbach’s α = 0.9).

BvFTD patients were divided according to the presence or absence of atrophy at baseline. A rating of ≥2 on any brain region was classified as ‘marked atrophy’. A score of 0 or 1 (questionable) across all areas of the scan was classified as ‘limited atrophy’. Twelve bvFTD patients were classified as showing marked atrophy (bvFTD-ma) and eight cases showed limited or no atrophy (bvFTD-la). Of the four cases with a C9ORF72 mutation, two were classified as bvFTD-la and two as bvFTD-ma.

**General cognitive assessment**

All patients received the Addenbrooke’s Cognitive Examination-Revised (ACE-R). The maximum is 100, and a score below 82 is suggestive of dementia.

**Socioemotional processing assessment**

**Ekman 60**

The Ekman 60 is a facial emotion recognition test where participants are shown faces expressing one of six basic emotions (anger, disgust, fear, sadness, surprise, happiness) on a computer screen, one at a time in pseudorandom order. Sixty pictures are shown in total, ten for each emotion. Participants are instructed to select the label that best matches the facial expression shown. The picture is shown for 5 s, although participants have unlimited time to respond. No feedback is provided. Administration time is approximately 10 min.

**The Awareness of Social Inference Test (TASIT)**

**Part A: emotion evaluation test**: Participants are presented with 28 short videotaped vignettes of everyday social interactions, each portraying one of six basic emotions (anger, revolted, anxious, happiness, sadness, surprise) or neutral emotion. After each clip, participants are instructed to determine the emotion portrayed and select the appropriate label on the response sheet. Administration time is approximately 20 min.

**Part B: social inference (minimal)**: Participants view 15 short videotaped vignettes of actors making sincere, sarcastic or paradoxically sarcastic statements. After each scene participants are asked four questions: (1) What is person 1 doing to the other person? (eg, “Is Ruth trying to pressure Gary into helping her?”) (2) What is person 1 trying to say to the other person? (eg, “Is she trying to say it’s OK if he doesn’t help her?”) (3) What is person 1 thinking? (eg, “Does she think he should stop what he is doing and help her?”) and (4) What is person 1 feeling? (eg, “Is she annoyed with him?”). For each question, the participant is required to respond ‘yes’, ‘no’ or ‘don’t know’. Participants could view the clips as often as necessary, and clarifications after any of the clips were provided without giving information about the emotion, sarcasm or mental states being portrayed. Administration time is approximately 20 min.

Prior to each socioemotional task, the researcher checked the participant was able to sufficiently understand the language demands of the task. Where any concerns about comprehension ability were raised, the participant was excluded from the study.

**Statistical analyses**

Data were analysed using SPSS V20.0 (IBM, Inc., Chicago, Illinois, USA). At baseline assessment, group differences were investigated using univariate analysis of variance (ANOVA), followed by post-hoc tests (Sidak correction multiple comparisons) for continuous variables or χ² tests where appropriate.
For the longitudinal analyses, linear mixed effects models were built to examine the changes in performance across groups over time. The fixed effects of the model included diagnostic category, follow-up time (calculated as days from first ACE-R assessment) and the interaction between diagnostic category and follow-up time. The only random effect included was the individual variability associated with a patient at baseline using the random intercept model. The variability of any estimated parameters was determined by the fixed and random components of the model. A significant effect of follow-up time indicates that performance on the variable of interest changes linearly over time, averaged across groups. In contrast, a significant interaction between diagnostic category and follow-up time indicates that the rate of change (slope) differs according to diagnosis. Residual errors of the model were assumed to be normally distributed, as were the random intercepts at baseline. All participants were assumed to be independent.

RESULTS

Aim 1: bvFTD versus AD
All groups were well matched for sex, age and education (all p values >0.05). In addition, no difference in the number of follow-up visits or the length of follow-up was observed between the bvFTD and AD groups (p values >0.05) On the FRS, AD patients were reported as having less functional impairment than bvFTD patients (p=0.017) (table 1).

At baseline, bvFTD and AD patients performed significantly lower than controls on the ACE-R, Ekman 60 and TASIT A tasks; however, no significant differences were observed between patient groups (table 2). On the TASIT B, only the bvFTD group was impaired at baseline performing below controls and AD patients on this task.

The modelled trajectories for scores on the ACE-R, Ekman 60, TASIT A and TASIT B are presented in table 3 and figure 1. Both bvFTD and AD declined on the ACE-R (F=13.380, p=0.001) and the Ekman 60 (F=3.985, p=0.05) over time; however, the rate of decline on these tasks was similar across diagnostic groups (F=0.743, p>0.05; F=0.913, p>0.05). On the TASIT A no significant pattern of decline was observed from baseline and the rate of decline also did not differ across groups (p>0.05). A trend for an interaction between diagnosis and follow-up time was however seen on the TASIT B (p=0.093), with the AD group showing faster decline than the bvFTD group on this task.

Aim 2: profiles of performance according to atrophy at baseline
To investigate whether different rates of decline were present within the bvFTD group, we divided bvFTD patients according to the level of atrophy present at baseline and compared the bvFTD-ma and bvFTD-la groups with AD patients. Again, all groups were well matched for sex, age and education (all p values >0.05). Furthermore, all patient groups were matched for disease duration, length of follow-up and number of visits (table 4). On the FRS, bvFTD-ma showed more severe functional impairments than AD patients (p=0.044), although no significant difference in severity was seen between bvFTD-ma and bvFTD-la patients (p>0.05). Cognitive profiles across groups are provided in the online supplementary information.

Significant differences were seen across all variables of interest at baseline, with bvFTD-ma, bvFTD-la and AD performing below controls on the ACE-R, the Ekman 60 and the TASIT Part B (table 5). Of note, the bvFTD-la group had a mean score of 82.9 on the ACE-R, which is above the cut-off for dementia of 82/100 on this measure. Posthoc analyses revealed no differences between patient groups on each of these tasks. In contrast, on the TASIT Part B, only the bvFTD-ma group differed from controls, and their performance was also impaired when compared with the AD group. No significant difference in performance was seen between the bvFTD-la and bvFTD-ma groups on the TASIT Part B (table 5).

Importantly, a different pattern of longitudinal decline emerged when bvFTD patients were compared with AD according to the degree of atrophy present at baseline (table 6, figure 2). On the ACE-R, a significant main effect of time was observed (F=12.974, p<0.001), but the diagnosis×time interaction was not significant (F=0.975, p>0.05), indicating that the rate of cognitive decline over time was similar across groups. In contrast,

### Table 1  Demographics at baseline and follow-up details for patient groups and controls

<table>
<thead>
<tr>
<th></th>
<th>bvFTD</th>
<th>AD</th>
<th>Control</th>
<th>F</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>18:2</td>
<td>13:4</td>
<td>18:6</td>
<td>1.78*</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.6±9.6</td>
<td>67.4±7.8</td>
<td>67.9±6.2</td>
<td>0.16</td>
<td>ns</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.2±3.3</td>
<td>13.3±3.4</td>
<td>13.5±2.5</td>
<td>1.11</td>
<td>ns</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.2±3.7</td>
<td>3.3±3.9</td>
<td></td>
<td>2.18</td>
<td>ns</td>
</tr>
<tr>
<td>FR (Rasch score)</td>
<td>0.1±1.2</td>
<td>1.2±1.2</td>
<td></td>
<td>6.36</td>
<td>0.017</td>
</tr>
<tr>
<td>Mean time of follow-up (years)</td>
<td>1.7±1.0</td>
<td>1.8±1.0</td>
<td></td>
<td>0.04</td>
<td>ns</td>
</tr>
<tr>
<td>Number of follow-up visits</td>
<td>2.7±0.7</td>
<td>2.9±0.9</td>
<td></td>
<td>1.16</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level.

### Table 2  Percent correct performance on the ACE-R and emotion processing tasks at baseline assessment in patient groups and controls

<table>
<thead>
<tr>
<th></th>
<th>bvFTD (n=20)</th>
<th>AD (n=17)</th>
<th>Control (n=24)</th>
<th>F</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>79.7±9.7</td>
<td>76.7±13.7</td>
<td>96.0±2.4</td>
<td>27.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SD</td>
<td>9.7</td>
<td>13.7</td>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-R</td>
<td>65.2±11.9</td>
<td>72.1±14.4</td>
<td>84.4±7.1</td>
<td>16.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ekman 60</td>
<td>62.7±17.0</td>
<td>70.6±13.0</td>
<td>83.5±6.8</td>
<td>15.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TASIT A</td>
<td>66.3±12.1</td>
<td>78.6±14.9</td>
<td>86.5±7.8</td>
<td>16.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TASIT B†</td>
<td>66.3‡</td>
<td>78.6</td>
<td>86.5±14.9</td>
<td>16.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*All scores are percent correct.

‡Significantly different from control group.

†Difference in atrophy significant.

AD, Alzheimer’s disease; bvFTD, behavioural-variant frontotemporal dementia; FRS, Frontotemporal Dementia Rating Scale; ns, non-significant.
on the Ekman 60, a main effect of time (F=4.083, p=0.048),
together with a trend for a diagnosis × time interaction, was
present (F=3.042, p=0.055), suggesting a faster rate of decline
in the bvFTD-ma group compared with other patient groups
(p=0.053) (table 6, figure 2). On the TASIT A, although no main
effect of time was observed (F=2.704, p>0.05), again, a trend
for an interaction between diagnosis and time was present
(F=2.704, p=0.062). Inspection of the model revealed that this
interaction was driven by the faster rate of decline in the
bvFTD-ma group than bvFTD-la and AD patients. Finally, on the
TASIT B, a significant main effect of time (F=6.680, p=0.015)
was present, indicating that averaged across groups, performance
declined on this task. Importantly, the diagnosis × time inter-
action was also significant (F=8.399, p=0.002), with the
bvFTD-ma and AD, but not bvFTD-la patients, declining on this
task over time (table 6, figure 2).

In summary, at baseline bvFTD and AD groups performed
worse than controls on the cognition and emotion recognition
tasks and performance was indistinguishable across patient
groups. In contrast, on the sarcasm detection task, only bvFTD
patients performed worse than controls and also performed
worse than AD patients. When bvFTD patients were divided
according to the level of brain atrophy present at baseline, a
similar pattern emerged. All patient groups were impaired on
the general cognition and emotion recognition tasks. Notably,
on the sarcasm detection task only the bvFTD-ma group was
impaired compared with controls, while the bvFTD-la group
performed within normal limits.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Follow-up</th>
<th>Diagnosis and follow-up</th>
<th>Parameter estimation, coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>p Value</td>
<td>F</td>
</tr>
<tr>
<td>ACE-R</td>
<td>13.4</td>
<td>0.001</td>
<td>0.7</td>
</tr>
<tr>
<td>Ekman60</td>
<td>4.0</td>
<td>0.050</td>
<td>0.9</td>
</tr>
<tr>
<td>TASIT A</td>
<td>1.0</td>
<td>0.336</td>
<td>0.2</td>
</tr>
<tr>
<td>TASIT B</td>
<td>3.0</td>
<td>0.093</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Parameter estimation coefficient indicates the change in percentage scores per annum according to diagnosis as estimated by the model. Values in bold indicate significant effects at p<0.05. Follow-up data available for 20 bvFTD and 17 AD on the ACE-R, Ekman 60, TASIT A, and 14 bvFTD and 6 AD on the TASIT B.

ACE-R, Addenbrooke’s Cognitive Examination-Revised; AD, Alzheimer’s disease; bvFTD, behavioural-variant frontotemporal dementia.
Longitudinal analyses revealed important differences in the rate of decline in bvFTD patients depending on the severity of brain atrophy at baseline. For general cognition, an overall decline was observed, with similar rates of decline across patient groups. On the emotion recognition and sarcasm tasks, the bvFTD-ma group typically declined at a faster rate than bvFTD-la and AD patients. In contrast, the bvFTD-la patients remained stable over time on the emotion recognition and sarcasm measures. The AD group declined on the sarcasm detection but not emotion recognition tasks (table 6, figure 2).

**DISCUSSION**

This study is the first to examine the rate of decline in socioemotional functioning in bvFTD and AD and to directly compare longitudinal performance of bvFTD patients who present with or without marked brain atrophy. The results confirm that socioemotional functioning is disproportionately affected in bvFTD-ma patients who display marked neuroimaging abnormalities at presentation. These findings further reveal for the first time that socioemotional processing continues to decline in this group at a faster rate compared with bvFTD-la patients who exhibit limited changes on brain imaging at presentation. In addition, this study suggests that, although bvFTD and AD patients experience declines in cognitive and socioemotional functioning over time, the pattern of decline appears to differ. bvFTD-ma patients experience rapid decline in general cognition, emotion recognition and sarcasm detection, whereas AD patients tend to show progressive decline in general cognition and sarcasm detection only. Here, we discuss the implications of our findings for improving the differential diagnosis of these syndromes and for understanding the prognosis of individuals diagnosed with bvFTD and AD.

Traditionally, episodic memory tasks have been used to differentiate between bvFTD and AD patients, with previous iterations of diagnostic criteria for bvFTD including memory impairment as an exclusionary criterion. Recently, however, evidence has demonstrated that a proportion of bvFTD patients present with significant alterations in memory, in some cases to a similar degree as seen in AD. Our results provide strong support for the assessment of socioemotional functioning, particularly the ability to understand sarcasm, rather than memory, to assist in clinically discriminating between bvFTD and AD. Sarcasm detection is associated with integrity of brain regions known to be crucial for emotion processing in FTD, including the orbitofrontal cortex, insula, amygdala and temporal pole, as well as the posterior parahippocampii and right medial frontal pole. Thus, the TASIT B test of sarcasm appears sensitive to early and progressive changes in mild bvFTD patients, providing further evidence of the clinical utility of sarcasm detection measures in the differential diagnosis of dementia. Because this task uses common everyday scenarios, it also provides a window into the alterations in interpersonal functioning these patients likely experience outside the clinic.

Preserved understanding of sarcasm in the early stage of AD is consistent with previous reports of maintained socioemotional functioning and preserved social graces in this disease. Crucially, this is the first time that decline in sarcasm detection over time has been demonstrated in AD despite emotion recognition remaining largely intact in this group. Importantly, despite increasing neuropathological changes, the ability to interpret complex social cues remained significantly better in...
AD than in bvFTD patients. The extent that other cognitive impairment contributes to the observed deficits in AD remains to be fully elucidated. Nevertheless, this finding is important for carers as social interactions may need to be modified over time so that individuals with AD can participate in these interactions in a meaningful way as their disease progresses.

In contrast to AD and bvFTD-ma patients, the bvFTD patients with limited brain changes at baseline showed minimal decline over time across all measures. This subset of bvFTD patients is becoming increasingly recognised. The few studies that have followed these bvFTD-la patients over time have reported only limited decline in general cognitive and functional abilities, which is consistent with our findings of stable cognitive and socioemotional functioning ability. The proportion of bvFTD-la patients who have true pathological FTD versus a clinical phenocopy of FTD is controversial. Prior studies have highlighted the following features as defining the phenocopy syndrome: lack of clinical progression over three or more years of follow-up, absence of atrophy on MRI, relatively normal performance on general cognitive screening tests and intact activities of daily living. Based upon these criteria, it is premature to classify our patients since their follow-up

---

### Table 6 Longitudinal analysis of outcome variables

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Follow-up time</th>
<th>Diagnosis and follow-up time interaction</th>
<th>Parameter estimation, coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>p Value</td>
<td>bvFTD-ma</td>
</tr>
<tr>
<td>ACE-R</td>
<td>13.0</td>
<td>&lt;0.001</td>
<td>1.0</td>
</tr>
<tr>
<td>Ekman60</td>
<td>4.1</td>
<td>0.048</td>
<td>3.0</td>
</tr>
<tr>
<td>TASIT A</td>
<td>2.7</td>
<td>0.106</td>
<td>3.0</td>
</tr>
<tr>
<td>TASIT B</td>
<td>6.7</td>
<td>0.015</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Parameter estimation coefficient indicates the change in percentage scores per annum according to diagnosis as estimated by the model. Values in bold indicate significant effects p < 0.05. Follow-up data available for 12 bvFTD-ma, 8 bvFTD-la and 17 AD on the ACE-R, Ekman60, TASIT A and 7 bvFTD-ma, 7 bvFTD-la and 6 AD on the TASIT B.

ACE-R, Addenbrooke’s Cognitive Examination-Revised; AD, Alzheimer’s disease; bvFTD-la, behavioural-variant frontotemporal dementia with limited brain atrophy; bvFTD-ma, behavioural-variant frontotemporal dementia with marked brain atrophy.

---

**Figure 2** Estimated marginal means based on the model showing percentage score changes on cognitive and emotion processing tasks in behavioural-variant frontotemporal dementia patients with limited and marked brain atrophy compared to Alzheimer’s disease patients. Error bars show 95% confidence intervals. Solid black line represents mean control score at baseline.
period was less than 3 years. The fact that they showed impairment on the ACE-R and in activities of daily living makes it more likely that they have slowly progressive bvFTD rather than the phenocopy syndrome. The aetiology of the phenocopy syndrome remains unclear. Some researchers have suggested that these individuals have Asperger’s syndrome or a developmental personality disorder and the observed symptoms are due to decompensation as life demands change. The identification of the genetic mutation C9ORF72 in some bvFTD patients with slow progression and less pronounced changes on neuroimaging suggests that a proportion of the patients labelled as the phenocopy syndrome have true FTD. In our study, however, the four positive C9ORF72 cases were equally likely to fall into the bvFTD-ma and bvFTD-la groups, suggesting that these cases show variable rates of progression and neuroimaging abnormalities (see also Ref. 39). Longer follow-up will be necessary to confirm this possibility. Finally, although our results suggest that the presence of a C9ORF72 mutation does not consistently predict emotion processing deficits, the number of patients who returned a positive result in this study was small. It will therefore be important to examine how genetic mutations are associated with different cognitive and socioemotional functioning profiles, and how these mutations predict the prognosis of patients affected by these disorders. Here, we have demonstrated that emotion recognition and sarcasm detection performance may help identify the subset of bvFTD patients who have a typical, progressive course.

Longitudinal studies comparing bvFTD and AD remain relatively rare, given the common issue of sample attrition with disease progression. Here, we have maximised the power of our study despite the relatively small sample size by employing mixed models analyses, which allow for variability in the time between assessments and accounts for missing data more effectively than other longitudinal approaches. These results suggest that the decline in emotion recognition ability in bvFTD-ma patients is most likely due to progressive atrophy in frontal and temporal brain regions crucial for supporting these complex abilities. Whether common or distinct regions contribute to decline in sarcasm detection in bvFTD and AD remains to be seen. Investigation of the relationship between progressive atrophy in frontal and temporal lobe regions and socioemotional functioning was unfortunately beyond the scope of this study. Studies that examine changes in brain structure over time using longitudinal neuroimaging analysis techniques will be crucial in confirming how progressive changes in the brain impact on sarcasm detection and emotion recognition ability in these dementia syndromes. In addition, the visual rating scale used here is simple, fast and reliable and therefore suitable for clinicians to adopt. It has excellent inter-rater reliability. The present study used only one rater, which resulted in a clear dichotomous split, but future studies may consider using a second rater to verify the presence of atrophy or use unbiased, automated neuroimaging techniques to classify groups.

The results from our study have implications for the clinical diagnosis and management of patients with bvFTD. Illness duration in bvFTD is highly variable, which is in part due to the different survival patterns seen in patients who present with and without brain atrophy. Here, we have demonstrated that incorporating socioemotional tasks into the assessment and diagnosis of these patients can assist clinicians in making a more accurate estimate of prognosis and assist in identifying those patients likely to show a typical rate of progression. Our results suggest that different disease mechanisms may underlie their similar clinical profile and therefore different treatment strategies may be necessary for these two subsets of bvFTD patients. From a management perspective, presence of socioemotional dysfunction undoubtedly contributes to the distressing and pervasive personality and behavioural changes seen in these patients and has a negative impact on levels of burden in carers.

Longitudinal studies of patients with dementia are crucial in understanding how different cognitive and emotional abilities become affected with disease progression. This study has revealed that bvFTD patients show an early and rapid decline in social and emotion processing, which is present across several clinical and experimental tasks. In addition, we have demonstrated that adoption of such socioemotional tasks can provide important clinical information that will help with the differential diagnosis and prognosis of younger-onset dementia syndromes. Furthermore, such objective information will help carers understand how these devastating disorders manifest, with a view to developing intervention strategies tailored to each of these disorders.

Acknowledgements The authors wish to thank the participants and their families for supporting their research and Associate Professor John Kwok and Dr Carol Dobson-Stone for the genetic analyses.

Contributors FK and OP were responsible for design, clinical data acquisition, analysis, interpretation and manuscript writing. MI was responsible for design, interpretation and manuscript writing. CL was responsible for analysis, interpretation and manuscript writing. LM and SL were responsible for design and manuscript writing. ED was responsible for design and manuscript writing. JRH was responsible for design, clinical data acquisition, interpretation and manuscript writing.

Funding This work was supported by a National Health and Medical Research Council (NHMRC) project grant (510106); the Australian Research Council (ARC) Centre of Excellence in Cognition and its Disorders (CE110001021); an ARC Discovery Early Career Research Award (DE130100463 to MI); the University of Sydney Thompson Fellowship (2012-02364 to SL); an ARC Federation Fellowship (FF0776229 to JRH); and an NHMRC Career Development Fellowship (APP1022684 to OP).

Competing interests None.

Ethics approval South Eastern Sydney Local Health District and the University of New South Wales.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We will consider sharing our data on request.

REFERENCES


Neurodegeneration

Tracking the progression of social cognition in neurodegenerative disorders

Emma Devenney, John R Hodges and Olivier Piguet

Fiona Kumfor, Muireann Irish, Cristian Leyton, Laurie Miller, Suncica Lah, John R Hodges and Olivier Piguet

Published online February 25, 2014

Updated information and services can be found at:
http://jnnp.bmj.com/content/early/2014/02/25/jnnp-2013-307098

These include:

Supplementary Material
Supplementary material can be found at:
http://jnnp.bmj.com/content/suppl/2014/02/25/jnnp-2013-307098.DC1.html

References
This article cites 37 articles, 7 of which you can access for free at:
http://jnnp.bmj.com/content/early/2014/02/25/jnnp-2013-307098#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Stroke (1414)
- Dementia (988)
- Drugs: CNS (not psychiatric) (1878)
- Memory disorders (psychiatry) (1352)
- Psychiatry of old age (331)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/