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Theory of mind impairment in patients with behavioural variant fronto-temporal dementia (bv-FTD) increases caregiver burden

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Abstract

Background: Theory of mind (ToM), the capacity to infer the intention, beliefs and emotional states of others, is frequently impaired in behavioural variant fronto-temporal dementia patients (bv-FTDp); however, its impact on caregiver burden is unexplored.
Setting: National Institute of Neurological Disorders and Stroke, National Institutes of Health.
Subjects: bv-FTDp ($n = 28$), a subgroup of their caregivers ($n = 20$) and healthy controls ($n = 32$).
Methods: we applied a faux-pas (FP) task as a ToM measure in bv-FTDp and healthy controls and the Zarit Burden Interview as a measure of burden in patients' caregivers. Patients underwent structural MRI; we used voxel-based morphometry to examine relationships between regional atrophy and ToM impairment and caregiver burden.
Results: FP task performance was impaired in bv-FTDp and negatively associated with caregiver burden. Atrophy was found in areas involved in ToM. Caregiver burden increased with greater atrophy in left lateral premotor cortex, a region associated in animal models with the presence of mirror neurons, possibly involved in empathy.
Conclusion: ToM impairment in bv-FTDp is associated with increased caregiver burden.

Keywords: *caregiver burden, theory of mind, faux-pas task, frontal cortex, voxel-based morphometry, older people*

Introduction

Behavioural variant fronto-temporal dementia (bv-FTD) is predominantly characterised by changes in social cognition and behaviour [1]. Theory of Mind (ToM) is the capacity to infer the intentions, beliefs and emotional states of others [2]. The neural signatures of ToM and bv-FTD overlap. Bv-FTD early atrophy involves the medial prefrontal cortex (mPFC), before extending into the frontal lobes, then temporal and parietal lobes [3], while the ToM network also includes medial and dorsolateral PFC (dlPFC), temporo-parietal junction, superior temporal sulcus and temporal pole [4]. A recent study further showed the involvement of sensorimotor regions in ToM [i.e. premotor cortex (PMC), inferior parietal lobule] [5].

The recognition of a faux-pas (FP) or a socially awkward comment [6] requires ToM [7]. Impairment in this task is associated with general behavioural impairment and indicates lack of empathy [8]. The association between patients' behavioural changes and caregiver burden is ambiguous [9–12]. Deficits in social cognition in particular present a challenge for caregivers of bv-FTD patients (bv-FTDp). A recent study showed that diminished empathy is associated with higher caregiver burden in semantic dementia, but not in Alzheimer's disease or bv-FTD [12]. In bv-FTD, higher burden is associated with right orbitofrontal gyrus atrophy

[13]. Nevertheless, the impact of ToM impairment on caregiver burden in bv-FTDp has not been investigated yet.

In this study, we employed a FP task to investigate ToM deficits in bv-FTDp and measured their effect on caregiver burden. We further used voxel-based morphometry (VBM) to examine the relationships between regional distributions of atrophy and ToM impairment and caregiver burden. We hypothesised that ToM impairment is associated with atrophy in nodes of the ToM network and that caregiver burden would increase with greater network atrophy.

Materials and methods

Participants

We enrolled a bv-FTD group ($n = 28$) [14], a subgroup of their caregivers ($n = 20$), healthy controls ($n = 18$) who completed the FP task (HC-FP) and another HC group ($n = 14$) who underwent MRI (HC-MRI). The Bv-FTD, HC-FP and HC-MRI groups were matched on age, education and gender (Table 1). All participants gave written informed consent, and the study was approved by the NINDS Institutional Review Board.

Clinical assessment

Neuropsychological assessments of bv-FTD and HC-FP groups included a measure of global cognitive function (Mattis Dementia Rating Scale, DRS-II, scaled score of the total performance with higher scores indicating greater cognitive ability) [15]. Intelligence was assessed by the National Adult Reading Test (NART) [16], in which participants are asked to pronounce 50 words (higher scores indicate greater intelligence), which correlated strongly with WAIS-full IQ in our bv-FTD group ($r = 0.52$, $P < 0.01$).

Experimental measures

The FP task was administrated to the bv-FTD and HC-FP groups. Participants read short stories and answered whether somebody said something inappropriate [6]. Percentages of correct answers were calculated for control questions (control score: CS) and FP questions (FP score: FPS). To assess caregiver burden, we used the overall score of the Zarit Burden Interview (ZBI) (see Supplementary data, Appendices S1–3 available in *Age and Ageing* online on the journal website http://www.ageing.oxfordjournals.org).

Behavioural data analysis

We used IBM© SPSS© (version 16 for Mac) and reported η^2 effect sizes (small ≥0.01, medium ≥0.06, large ≥0.14) only for significant results ($P < 0.05$, two tailed). We used an independent *t*-test to compare bv-FTD and HC-FP on the clinical assessment (DRS-II scaled score and NART total score).

Since HC-FP and bv-FTD groups differed significantly on intelligence (HC-FP had higher NART scores) and gender (fewer females in bv-FTD), we applied a 2 × 2 analysis of covariance (ANCOVA) on FP performance with Condition (CS, FPS) as a within-subjects factor, Group (bv-FTD, HC-FP) as a between-subjects factor, and intelligence and gender as covariates. We also ran bivariate Pearson's correlations to examine the relationship between bv-FTD performance and caregiver burden.

Neuroimaging acquisition and analysis

The neuroimaging analysis is described in detail in the Supplementary data (Appendix S4 available in *Age and Ageing* online). We first compared total intracranial volume (TIV), ventricular size, grey matter and white matter between bv-FTD and HC-MRI groups, using independent-samples *t*-tests [family wise error (FWE) correction; $P < 0.001$, two tailed; threshold of 50 voxels]. After creating a mask of significant grey matter differences between groups, we ran a linear regression model to examine the relationship between regions of atrophy and bv-FTD FP performance ($P < 0.001$, two tailed, uncorrected; threshold of 50 voxels), entering FP performance as a regressor and age, education, gender, TIV, and NART as confounds. Finally, we performed bivariate Pearson's correlations between participants' overall burden score and intensity values at the peak voxels of significant atrophy clusters in the ToM network.

Results

Clinical assessment

The bv-FTD group performed significantly worse than the HC-FP group on global cognition (DRS-II) and intelligence (NART) (Table 1).

Behavioural results

The ANCOVA on FP performance revealed no main effect for intelligence [$F(1,42) = 1.73$, $P = 0.20$] or gender [$F(1,42) = 0.05$, $P = 0.819$], but main effects for Condition [$F(1,42) = 4.44$,

Table 1. Descriptive [mean, (s.d.)] and inferential statistics of demographics and clinical assessment of bv-FTD, HC-FP and HC-MRI groups.

	Bv-FTD	HC-FP	HC-MRI	Statistics
Age (years)	59.18 (1.79)	60.33 (2.07)	60.57 (1.70)	$F(2,58) = 0.18$, $P = 0.838$
Education (years)	15.89 (0.64)	15.08 (0.39)	17.14 (0.93)	$F(2,58) = 1.92$, $P = 0.156$
Gender female:male	8:20	10:8	7:7	$\chi^2(1) = 3.07$, $P = 0.080$
NART (total score)	28.61 (1.43)	37.39 (1.93)		$t(44) = -3.73$, $P < 0.001$
DRS-II (scaled score)	4.57 (0.57)	12.00 (0.47)		$t(44) = -9.25$, $P < 0.001$

NART, National Adult Reading Test; DRS, Mattis Dementia Rating Scale.

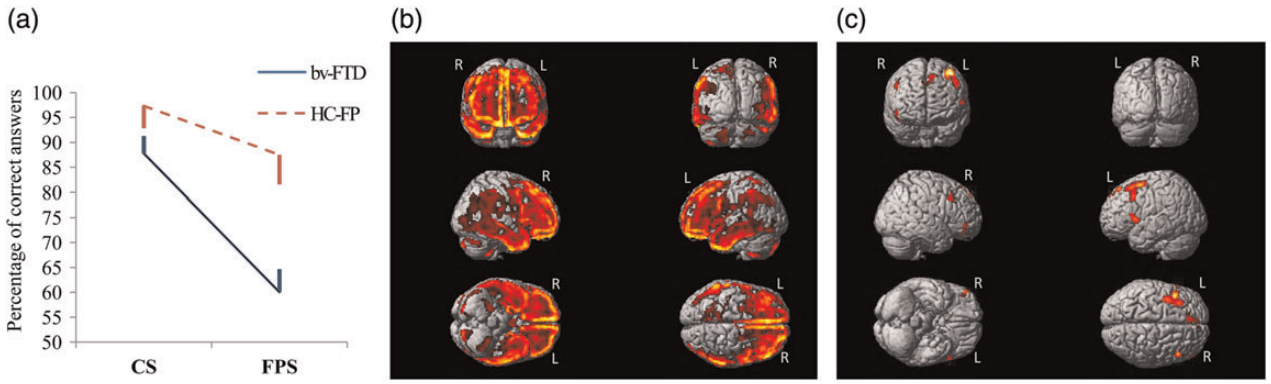

Figure 1. (a) Faux-pas performance (percentage of correct answers ± s.e.m). The bv-FTD group performed significantly worse than the HC-FP group for FPS but not for CS. (b) VBM analysis, grey matter atrophy in bv-FTD group. Patterns of significant greater grey matter loss identified in bv-FTD group than in the HC-MRI group (FWE-corrected $P < 0.001$, minimum cluster size 50 voxels). (c) VBM analysis. Grey matter atrophy associated with FP performance. Regions of significantly reduced grey matter density associated with FPS in bv-FTDp ($P < 0.001$ uncorrected; minimum cluster size 50 voxels): the right dlPFC (Talairach: $x = 52$, $y = 22$, $z = 38$; BA9), right OFC (52, 6, 6; BA47), left lateral PMC (–40, 6, 62; BA6), left medial PMC (–6, 42, 54; BA8) and left STC (–50, 10, 2; BA22).

$P = 0.041$, $\eta^2 = 0.096$] and Group [$F(1,42) = 7.15$, $P = 0.011$, $\eta^2 = 0.145$], and a significant interaction for Condition × Group [$F(1,42) = 9.71$, $P < 0.01$, $\eta^2 = 0.188$). Follow-up one-way ANCOVAs on FP performance (CS, FPS), with Group (bv-FTD, HC-FP) as a between-subjects factor, intelligence and gender as covariates, showed a group difference for FPS [$F(1,42) = 10.78$, $P < 0.01$, $\eta^2 = 0.204$], but not for CS [$F(1,42) = 1.92$, $P = 0.173$]. This indicated that the bv-FTD group was more impaired on the FPS (but not CS) compared with the HC-FP group (Figure 1a). Bivariate Pearson's correlations showed a significant correlation between caregiver burden and FPS ($r = -0.54$, $P < 0.01$) but not CS ($r = -0.28$, $P = 0.228$), indicating that caregiver burden was positively associated with FP impairment (see Supplementary data, Appendices S5–6 available in *Age and Ageing* online for analyses showing the unique relationships between burden and ToM impairments).

Neuroimaging results

Whole-brain volume analysis showed a significant reduction in grey matter [$t(39) = 5.22$, $P < 0.001$] and white matter [$t(39) = 4.31$, $P < 0.001$] volumes in the bv-FTD compared with HC-MRI group (Figure 1b). Ventricular size showed a reverse pattern [$t(39) = 5.10$, $P < 0.001$]. The linear regression model analysis revealed significant relationships between FP performance and the right dlPFC, right orbitofrontal cortex (OFC), left lateral PMC, left medial PMC and left superior temporal cortex (STC) (Figure 1c). Caregiver's overall burden was significantly associated with voxel density in the left lateral PMC ($r = -0.51$, $P < 0.05$, Bonferroni corrected), suggesting that greater atrophy in lateral PMC led to greater caregiver burden.

Discussion

We investigated ToM in bv-FTD and its impact on caregiver burden. As predicted, ToM impairment was associated with higher caregiver burden and with atrophy in regions of the ToM network. Caregiver burden increased with greater atrophy in the left lateral PMC.

We employed whole-brain VBM analysis and showed significant association between ToM impairment and atrophy in the right dlPFC, right OFC, left lateral and medial PMC, and left STC. Although the ToM network consistently includes medial PFC, temporo-parietal junction and anterior temporal lobes, recent literature highlights a broader network [17, 18]. Our findings are consistent with a previous region of interest VBM study, showing involvement of the frontal cortex (vmPFC, dlPFC) [8], and previous neuroimaging studies showing engagement of frontal [4], paralimbic/limbic and temporal areas in ToM [9]. In particular, links have been found between OFC and inhibitory processes and regulation of emotional responses [19]; dlPFC and cognitive control [20]; left STC and language comprehension; and PMC and the selection and planning of movement [21]. The fact that, in our study, FP performance was not associated with the main classic ToM brain network could be explained by a third factor driving FP performance (e.g. empathy).

Our study is the first to suggest that ToM impairment in bv-FTD patients leads to greater caregiver burden. It confirms the impact of behavioural changes on caregiver burden and provides a specific metric that is deeply ingrained in the patients' and caregivers' daily lives. As a consequence of a ToM deficit, social interactions between caregivers and bv-FTDp, as well as outside social engagements, might be more stressful leading to a reduction in joint activities [11]. It is possible that this association is due to other factors; here, we controlled for bv-FTDp's intelligence and global cognition.

Moreover, caregiver burden increased with greater atrophy in the left lateral PMC. The PMC plays a key role in the preparation of actions [21]. The lateral PMC together with dlPFC is associated with goal-directed behaviours [22]. Evidence in animal models indicates that the PMC contains

mirror neurons. The mirror neuron system is involved in empathy [5, 20] and is complementary to the ToM system [23]. We propose that mirror neurons are activated in the recognition of FPs, triggering simulation of the actions and the feelings of the character [24].

The association between ToM, brain areas and burden might be driven by factors we could not control, such as motor skills, which is a limitation of our study. The interpretation of the association between PMC and burden is speculative (e.g. many functions are associated with this region). Also, VBM analyses only grey and white matter volumes. Further analyses of surface area, gyrification or cortical thickness using FreeSurfer could be performed in a follow-up study.

In conclusion, ToM impairment is a prominent symptom in bv-FTDp, which significantly affects caregivers. In bv-FTD, atrophy in the left lateral PMC is associated with increased burden in caregivers. Interventions aimed at improving ToM in bv-FTDp may help relieve the caregiver of some of the burden of social chaperoning and also improve the patient's understanding of the intentions of caregivers and others.

Key points

- ToM is frequently impaired in FTDp.
- ToM impairment affects caregiver burden.
- ToM is a social skill.

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Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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