Right anterior temporal lobe dysfunction underlies theory of mind impairments in semantic dementia

Muireann Irish,1,2,3 John R. Hodges2,3,4 and Olivier Piguet2,3,4

1 School of Psychology, the University of New South Wales, Sydney, Australia
2 Neuroscience Research Australia, Randwick, Sydney, Australia
3 Australian Research Council Centre of Excellence in Cognition and its Disorders, Sydney, Australia
4 School of Medical Sciences, the University of New South Wales, Sydney, Australia

Correspondence to: Dr. Muireann Irish, Neuroscience Research Australia, Barker Street, Randwick, Sydney, NSW 2031, Australia
E-mail: m.irish@neura.edu.au

Semantic dementia is a progressive neurodegenerative disorder characterized by the amodal and profound loss of semantic knowledge attributable to the degeneration of the left anterior temporal lobe. Although traditionally conceptualized as a language disorder, patients with semantic dementia display significant alterations in behaviour and socioemotional functioning. Recent evidence points to an impaired capacity for theory of mind in predominantly left-lateralized cases of semantic dementia; however, it remains unclear to what extent semantic impairments contribute to these deficits. Further the neuroanatomical signature of such disturbance remains unknown. Here, we sought to determine the neural correlates of theory of mind performance in patients with left predominant semantic dementia (n = 11), in contrast with disease-matched cases with behavioural-variant frontotemporal dementia (n = 10) and Alzheimer’s disease (n = 10), and healthy older individuals (n = 14) as control participants. Participants completed a simple cartoons task, in which they were required to describe physical and theory of mind scenarios. Irrespective of subscale, patients with semantic dementia exhibited marked impairments relative to control subjects; however, only theory of mind deficits persisted when we covaried for semantic comprehension. Voxel-based morphometry analyses revealed that atrophy in right anterior temporal lobe structures, including the right temporal fusiform cortex, right inferior temporal gyrus, bilateral temporal poles and amygdalae, correlated significantly with theory of mind impairments in the semantic dementia group. Our results point to the marked disruption of cognitive functions beyond the language domain in semantic dementia, not exclusively attributable to semantic processing impairments. The significant involvement of right anterior temporal structures suggests that with disease evolution, the encroachment of pathology into the contralateral hemisphere heralds the onset of social cognitive deficits in this syndrome.

Keywords: frontotemporal dementia; semantic memory; social cognition; anterior temporal lobe; theory of mind
Abbreviations: ACE-R = Addenbrooke’s Cognitive Examination-Revised; FTD = frontotemporal dementia; ToM = theory of mind

Introduction

A fascinating aspect of human cognition is the innate capacity to infer the thoughts, feelings, beliefs and intentions of others, known as theory of mind (ToM). Our unique aptitude to spontaneously consider perspectives distinct from our own is fundamental to successful social interactions, enabling us to describe, explain and predict behaviour based on the mental states of others (Baron-Cohen, 1995).

Given the multifaceted nature of mental state attribution, it is not surprising that a distributed neural network has been found to underlie successful ToM performance including the tempo-parietal
junction (Saxe and Wexler, 2005), the posterior superior temporal sulci, the precuneus, the anterior temporal lobes (Olson et al., 2007) and medial prefrontal cortices (Amodio and Frith, 2006). Functional neuroimaging studies of ToM have consistently revealed robust activation of the medial prefrontal cortices when healthy individuals mentalize to consider another person’s psychological perspective (Castelli et al., 2000; Gallagher and Frith, 2003; Amodio and Frith, 2006). The prominence of the prefrontal cortex in facilitating ToM performance is further underscored by lesion studies in which selective damage to these brain regions impacts dramatically upon the capacity to understand and infer the thoughts and beliefs of others (Stuss et al., 2001; Lee et al., 2010; Roca et al., 2011).

Increasingly, research efforts are directed towards understanding the neuroanatomical substrates of ToM by studying how the characteristic patterns of neural degeneration seen in neurodegenerative conditions impacts upon this complex cognitive process (Poletti et al., 2012). Of particular relevance in this context is the observation of profound disruption of socioemotional functioning in the behavioural variant of frontotemporal dementia (FTD), a neurodegenerative disorder characterized by the progressive degeneration of the medial prefrontal and frontoinsular cortices (Rabinovici et al., 2007; Seeley et al., 2008). Changes in inhibitory control, loss of empathy, emotion dysregulation, violation of social norms, and loss of insight are pervasive and characteristic features of this dementia syndrome (Piguet et al., 2011; Rascovsky et al., 2011). Importantly, it has been suggested that the impairments in socially oriented behaviour in behavioural variant FTD reflect the specific disruption of ToM abilities (Gregory et al., 2002; Kipps and Hodges, 2006). This hypothesis is well supported by a range of experimental studies in which marked impairments in ToM have been documented in behavioural variant FTD on false-belief tasks (Gregory et al., 2002; Eslinger et al., 2007; Fernandez-Duque et al., 2009; Le Bouc et al., 2012; Shany-Ur et al., 2012), simple cartoon tasks requiring social inference (Snowden et al., 2003; Lough et al., 2006), and tests of faux pas recognition (Torralva et al., 2007, 2009; Gleichgerrcht et al., 2011; Funkiewiez et al., 2012). Such deficits in ToM processing have been found to correlate significantly with predominantly right hemisphere structures including the orbitofrontal cortex, lateral temporal cortices, as well as visual association cortices and the posterior cingulate cortex (Eslinger et al., 2007).

The suggestion that the integrity of temporal lobe structures may be essential for successful social functioning is not new (Rankin et al., 2006; Olson et al., 2007; Zahn et al., 2009a), but surprisingly few studies have investigated the role of the temporal lobes in ToM performance. The syndrome of semantic dementia offers a unique opportunity to explore how the progressive disintegration of the conceptual knowledge base impacts on the capacity for ToM. The clinical profile of semantic dementia is dominated by the progressive and amodal loss of semantic knowledge attributable to the degeneration of the anterior temporal lobes (Hodges and Patterson, 2007; Mion et al., 2010). This loss of conceptual knowledge may reflect the disruption of a central semantic hub (Patterson et al., 2007) or, alternatively, the degeneration of a temporosylvian language network for verbal concepts (Snowden et al., 2004; Mesulam et al., 2013) within a broadly distributed neural network (Binder et al., 2009). Importantly, patients with semantic dementia present with relative sparing of other cognitive functions, such as everyday memory and visuospatial skills, at least in the early stages of the disease (Hodges and Patterson, 2007). Although a large corpus of research has demonstrated marked ToM impairments in behavioural variant FTD, experimental evidence regarding the capacity for ToM in semantic dementia is sparse (Irish et al., 2012b). Patients with semantic dementia are typically reported to show socioemotional disturbances, presenting as cold-hearted, self-centred, and lacking in empathy (Rankin et al., 2005, 2006; Hodges and Patterson, 2007). Interestingly, lateralization of temporal lobe atrophy may be a critical factor, as changes in social conduct and personality are well documented in cases with FTD with predominant atrophy to right temporal structures (Edwards-Lee et al., 1997; Chan et al., 2009), and seem particularly striking in those rare cases with semantic dementia who present with predominantly right lateralized patterns of temporal lobe atrophy (Perry et al., 2001; Irish et al., 2013; Henry et al., 2014). The observation of abnormally egocentric behaviour in semantic dementia has been suggested to relate, in part, to alterations in the capacity for ToM (Duval et al., 2012).

Despite these well-documented changes in social cognition in semantic dementia, to date, only two studies have empirically investigated ToM in this syndrome. Eslinger et al. (2007) reported significant deficits in identifying the thoughts and feelings of cartoon characters in social situations in a mixed sample of semantic dementia and progressive non-fluent aphasic cases. More recently, Duval et al. (2012) demonstrated marked impairments across cognitive and affective measures of ToM in a sample of patients with left-predominant semantic dementia and suggested that these deficits related to the patients’ characteristic left temporal lobe hypometabolism, although this relationship was not directly examined. Accordingly, although the available evidence points towards altered ToM processes in semantic dementia, the neuroanatomical signature of such deficits remains to be delineated.

The aims of the present study were two-fold. Firstly, we wished to investigate the capacity for mental state attribution in a well-characterized sample of patients with left-predominant semantic dementia using a simple ecologically valid task, and to contrast their performance with that of patients with behavioural variant FTD and those with Alzheimer’s disease. Patients with behavioural variant FTD were included as a comparison disease group given their well-characterized deficits in ToM processing, whereas patients with Alzheimer’s disease were included as a disease control group outside of the frontotemporal lobar degeneration spectrum, in which variable, but generally mild, alterations in ToM have been documented (Castelli et al., 2011; Le Bouc et al., 2012). Secondly, we wished to establish the neuroanatomical signature of ToM impairments in semantic dementia using whole-brain voxel-based morphometry analyses and to contrast the regions implicated in ToM dysfunction in semantic dementia with those implicated in behavioural variant FTD.
Materials and methods

Participants

Thirty-one patients with dementia (behavioural variant FTD = 10; semantic dementia = 11; Alzheimer’s disease = 10) and 14 age- and education-matched healthy control subjects were recruited through FRONTIER at Neuroscience Research Australia, Sydney. All patients with dementia met the relevant clinical diagnostic criteria for semantic dementia (also known as semantic variant primary progressive aphasia; Gorno-Tempi et al., 2011), behavioural variant FTD (Rascovsky et al., 2011), and Alzheimer’s disease (McKhann et al., 2011). Patient diagnoses were established by consensus among senior neurologist, neuropsychologist, and occupational therapist based on extensive clinical investigations, cognitive assessment and structural brain neuroimaging. Briefly, all cases with semantic dementia presented with left dominant anterior temporal lobe atrophy profiles on structural MRI and exhibited progressive loss of word meaning with significant naming and comprehension impairments, and relatively intact everyday memory. Cases with semantic dementia presenting with atypical features, notably prosopagnosia and right dominant atrophy profiles, were not included in this study. Patients with behavioural variant FTD presented with decline in behaviour and interpersonal functioning, accompanied by loss of insight, increased apathy and emotional blunting. Finally, patients with Alzheimer’s disease displayed significant episodic memory loss in the context of preserved personality and behaviour. The functional status of patients was determined using the Frontotemporal Dementia Functional Rating Scale (Mioshi et al., 2010), which is a dementia staging tool sensitive to changes in functional abilities and neuropsychiatric symptomatology. Healthy control subjects were recruited from a local volunteer research panel and local community clubs. All controls scored 0 on the Clinical Dementia Rating scale (Morris, 1997), and ≥88 on the Addenbrooke’s Cognitive Examination-Revised (ACE-R; Mioshi et al., 2006).

Exclusion criteria for all participants included prior history of mental illness, significant head injury, movement disorders, alcohol and other drug abuse, and limited English proficiency. Further, the MRI scans for all potential participants were reviewed by an experienced radiologist for the presence of white matter hyperintensities or significant cerebrovascular disease. Ethical approval for this study was obtained from the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales ethics committees. All participants, or their person responsible, provided informed consent in accordance with the Declaration of Helsinki.

General cognitive assessment

Overall cognitive functioning was assessed using the ACE-R (Mioshi et al., 2006), which comprises subscales measuring orientation, verbal memory, fluency, language and visuospatial functioning. Verbal episodic memory was assessed using the Memory subscale of the ACE-R, whereas non-verbal episodic recall and recognition was measured using the recall component of the Rey Complex Figure (Meyers and Meyers, 1995) and the Doors and People Test Part A (Baddeley et al., 1994), respectively. For Rey Complex Figure performance, a percentage retained score was calculated (recall score / copy score × 100), to control for possible organizational and planning demands of the task. Executive functioning was assessed using the Trail Making Test (Parts B-A; Reitan, 1958), and Digit span backwards (Wechsler, 1997). Verbal semantic performance was assessed using verbal letter fluency (F, A, S; Strauss et al., 2006), and the Naming and Comprehension subtests from the Sydney Language Battery (Savage et al., 2013). Briefly, the Sydney Language Battery Naming subscale assesses single-word processing, in which participants are required to provide the correct names in response to living and non-living colour visual stimuli of increasing difficulty. The Sydney Language Battery Comprehension subscale is a word–picture matching task that uses the same stimuli as in the Naming task. Participants are asked to select the picture that best matches the word spoken by the examiner from an array of photographs containing the target item and six conceptually or visually related lures. Visuospatial functioning was assessed using the visuospatial subscale from the ACE-R. Finally, spouses of participants completed the Perspective Taking and Empathic Concern subscales of the Interpersonal Reactivity Index (Davis, 1983) as an index of an individual’s current level of socioemotional functioning. Perspective Taking questions measure the ability of the patient to imagine the cognitive perspective of another person, whereas the Empathic Concern subscale assesses the capacity to perceive another person’s emotional state.

Assessment of theory of mind

The procedure for this study has been described in detail elsewhere (Lough et al., 2006). Briefly, we used a cartoon task that dissociates between physical and ToM understanding of humorous scenarios. Participants were shown two sets of cartoon jokes, each of which comprised 10 pictures. One set of jokes could be understood purely in physical terms (e.g. the man hits his friend over the head with a sledgehammer to remove a bee). The other set of jokes, however, required participants to infer the mental state of the main characters to convey the humour of the scenario (e.g. the man thinks he is being held up, but doesn’t realize the gun is just an umbrella). The physical and ToM cartoons were presented in pseudo-random order to participants with the instruction to describe why someone might find the cartoon scene funny. No time limit was imposed for each cartoon, and general prompting was provided to ensure that the participants remembered the instructions of the task (e.g. ‘Why might someone find this picture funny?’). Each cartoon was awarded 1 point if, (i) for physical cartoons, participants adequately conveyed the humour of the scenario, over and above the simple naming or identification of elements in the scene; and (ii) for ToM cartoons, participants used language that indicated that they had adequately perceived the mental state inferred in the cartoon, (e.g. ‘he thinks’, ‘she does not know’, ‘they believe that’). Thus, the total score for each set of cartoons was 10 points. The scoring system was designed to ensure that patients with semantic dementia would not be overly penalized by the presence of anomia. For the Physical cartoons, a response was deemed acceptable when patients provided an adequate description of the overall humour of the scene, despite naming omissions or errors. On the ToM cartoons, specific theory of mind language, irrespective of anomia, was essential to warrant a score of 1 point. See Supplementary material for detailed examples of scoring of Physical and ToM trials in semantic dementia.

Statistical analyses

Demographic and cognitive data were analysed using IBM SPSS Statistics (Version 21.0). Multivariate analyses of variance (MANOVA) with Sidak post hoc tests were used to explore main effects of group (control subjects, behavioural variant FTD, semantic dementia, Alzheimer’s disease) for all general cognitive tests. The rationale for using Sidak modification of the traditional Bonferroni post hoc test is that the statistical power of the analyses is not affected,
whereas the flexibility of the original Bonferroni method is maintained (Keppel and Wickens, 2004). Performance on the Cartoons task was analysed using a repeated-measures MANOVA to explore main effects of condition (Physical, ToM) and group, as well as relevant interactions. Pearson R correlations, corrected for multiple comparisons at $P < 0.01$, were run to explore potential relationships between performance on the cartoons task with neuropsychological test measures. Chi-squared tests ($X^2$), based on the frequency patterns of dichotomous variables (e.g. sex), were also used.

**Results**

### Demographics

The groups were well matched for age ($P = 0.286$) and education ($P = 0.103$). Sex was not equally distributed between the groups [$X^2(3) = 10.830, P = 0.013$] as patient groups comprised more male than female participants compared with control subjects. Importantly, the patient groups were matched for disease duration (i.e. months elapsed since onset of symptoms, $P = 0.636$). Patients with behavioural variant FTD showed significantly higher levels of functional impairment relative to patients with Alzheimer’s disease on the Frontotemporal Dementia Functional Rating Scale ($P = 0.010$), however, no significant differences in functional impairment were evident between the behavioural variant FTD and semantic dementia patient groups ($P = 0.136$).

### General cognitive functioning

Neuropsychological testing revealed characteristic profiles in each patient group (Table 1). Briefly, all patient groups were significantly impaired on the ACE-R, $F(3,41) = 21.578, P < 0.0001$ with respect to control subjects (behavioural variant FTD, $P = 0.005$; semantic dementia, $P < 0.0001$; Alzheimer’s disease, $P = 0.003$). In addition, semantic dementia patients showed disproportionate deficits on the ACE-R compared with behavioural variant FTD ($P = 0.001$) and Alzheimer’s disease ($P = 0.003$), most likely because of the verbal loading of this task. No significant difference was evident between Alzheimer’s disease and patients with behavioural variant FTD on this measure.

Looking at each group separately, the neuropsychological profile of the semantic dementia group was dominated by severe semantic impairments on verbal letter fluency ($P < 0.0001$), Naming ($P < 0.0001$) and Comprehension ($P < 0.0001$) measures in the context of relatively preserved executive function (Trails, $P = 0.936$; Digit span backwards, $P = 0.992$). Although deficits in verbal episodic memory were evident (ACE-R Memory, $P < 0.0001$), no significant differences were evident between patients with semantic dementia and control subjects on tests of non-verbal episodic memory (Rey Complex Figure % retained, $P = 0.993$; Doors Part A, $P = 0.174$). Finally, visuospatial functioning was also found to be in line with control subject performance in the semantic dementia group (ACE-R Visuospatial subscale, $P = 0.652$).

Patients with behavioural variant FTD displayed significant Naming impairments ($P = 0.009$) in the context of relatively intact Comprehension ($P = 0.304$) and Visuospatial functioning (ACE-R Visuospatial, $P = 0.315$) relative to control subjects. Further deficits were evident in the behavioural variant FTD group for verbal fluency ($P < 0.0001$) and verbal (ACE-R Memory, $P = 0.045$) and visual (Rey Complex Figure % retained, $P = 0.028$; Doors Part A, $P = 0.043$) episodic memory. Although no significant differences were evident between behavioural

### Voxel-based morphometry analysis

A voxel-wise general linear model was employed to investigate grey matter intensity differences through permutation-based non-parametric testing (Nichols and Holmes, 2002) with 5000 permutations per contrast. Differences in cortical grey matter volumes between patients (behavioural variant FTD, semantic dementia, and Alzheimer’s disease) and control subjects were assessed using $t$-tests. Next, correlations between performance on the theory of mind task and regions of grey matter atrophy were investigated in each FTD patient group, combined with control subjects (i.e. semantic dementia and control subjects; behavioural variant FTD and control subjects).

This procedure was adopted to increase the study’s statistical power to detect brain–behaviour relationships across the entire brain by achieving greater variance in behavioural scores (Pollack et al., 2009; Irish et al., 2012a). For additional statistical power, a covariate only statistical model with a [1] $t$-contrast was used, providing an index of association between decreasing grey matter volume and lower scores on the experimental task. Age was included as a nuisance variable in the covariate analyses. An unbiased whole-brain approach was used across all atrophy and covariate VBM analyses. Anatomical locations of significant results were overlaid on the MNI standard brain, with coordinates of maximum change provided in MNI stereotaxic space. Anatomical labels were determined with reference to the Harvard-Oxford probabilistic cortical atlas.
variant FTD and control subjects on the Trail Making Task ($P = 0.125$), patients with behavioural variant FTD showed significant impairments for Digit span backwards ($P = 0.021$).

Finally, patients with Alzheimer’s disease demonstrated characteristic deficits across tests of verbal (ACE-R Memory, $P < 0.0001$) and visual (Rey Complex Figure % retained, $P = 0.010$; Doors Part A, $P = 0.004$) episodic memory. Further impairments were evident for semantic Naming ($P = 0.041$), verbal letter fluency ($P = 0.053$), and executive functioning (Trail Making Task, $P = 0.005$; Digits backwards, $P = 0.008$) relative to control subjects. Visuospatial functioning (ACE-R Visuospatial, $P = 0.416$) and semantic Comprehension ($P = 0.593$) were not found to differ significantly from control subjects.

**Interpersonal functioning**

Caregiver ratings of interpersonal functioning on the Interpersonal Reactivity Index revealed significant overall group differences for perspective taking ($F(3,41) = 7.926, P < 0.0001$) and empathic concern ($F(3,41) = 6.182, P = 0.002$). Patients with semantic dementia were rated as displaying significant alterations across perspective taking ($P < 0.0001$) and empathic concern ($P = 0.004$) subscales relative to control subjects. Patients with behavioural variant FTD showed a similar profile of socioemotional disturbance (perspective taking; $P = 0.014$; empathic concern; $P = 0.010$), whereas patients with Alzheimer’s disease were rated only as showing perspective taking difficulties ($P = 0.050$) with no significant alterations documented for empathic concern ($P = 0.577$) relative to control subjects. No significant differences were evident between semantic dementia and patients with behavioural variant FTD for perspective taking or empathic concern functioning (all $P$-values $> 0.7$).

**Performance on the cartoons task**

Table 2 and Fig. 1 illustrate overall performance on the Physical and ToM subscales of the Cartoons task. A repeated measures multivariate ANOVA revealed a main effect for group [$F(3,41) = 30.205, P < 0.0001$], which reflected the fact that irrespective of condition, overall performance was significantly lower in patients compared with control subjects (behavioural variant FTD, $P < 0.0001$; semantic dementia, $P = 0.0001$; Alzheimer’s disease, $P = 0.022$). A main effect for Condition [$F(1,41) = 77.656, P < 0.0001$] was also evident, in which performance on the Physical subscale was significantly higher than on the ToM subscale ($P < 0.0001$). Further, a significant Group × Condition interaction was found [$F(3,41) = 8.994, P < 0.0001$]. Sidak post hoc tests revealed that on the Physical subscale, all patient groups
were impaired with respect to control subjects (behavioural variant FTD, $P < 0.0001$; semantic dementia, $P < 0.0001$; Alzheimer’s disease, $P = 0.046$). In contrast, however, on the ToM subscale, only patients with behavioural variant FTD and those with semantic dementia showed impairments (all $P$-values $< 0.0001$), with no statistically significant difference evident between patients with Alzheimer’s disease and control subject performance ($P = 0.075$).

Within-patient group contrasts further revealed differences between conditions. Control, behavioural variant FTD, and semantic dementia participants scored significantly lower on the ToM subscale in comparison with the Physical subscale (control, $P = 0.007$; behavioural variant FTD, $P < 0.0001$; semantic dementia, $P < 0.0001$), in contrast with the Alzheimer’s disease group, in which performance did not differ significantly across conditions ($P = 0.080$).

### Correlations between theory of mind performance and neuropsychological test measures

For patients with semantic dementia, Physical scores were significantly associated with Comprehension performance ($r = 0.744, P = 0.009$); however, this relationship was not evident on the ToM subscale. Similarly, Physical and ToM subscales were not found to correlate in the semantic dementia group. In contrast, the Physical and ToM subscales were highly correlated in the behavioural variant FTD group ($r = 0.814, P = 0.004$) with no other significant relationships observed. Significant associations were not evident between caregiver ratings of perspective taking and empathic concern on the Interpersonal Reactivity Index and ToM performance in the semantic dementia or behavioural variant FTD groups (Table 3). In the control and Alzheimer’s disease groups, no significant relationships were evident between either the Physical or ToM subscales and the neuropsychological test measures.

### Semantic processing and Theory of Mind performance

Given that successful performance of the Cartoons task may, in part, depend on comprehension of the scenes, we repeated the analyses to include the Comprehension subtest from the Sydney Language Battery (Savage et al., 2013) as a covariate to control for general comprehension and language processing (Fig. 2). This covariate analysis was important given the disproportionate Comprehension deficits in patients with semantic dementia compared with the other patient groups (behavioural variant FTD, $P < 0.0001$; Alzheimer’s disease, $P < 0.0001$). The overall main effect for group persisted [$F(3,36) = 15.160, P < 0.0001$], with global impairments evident exclusively in the behavioural variant FTD group ($P < 0.0001$), with semantic dementia and Alzheimer’s disease patients scoring in line with control overall performance (semantic dementia, $P = 0.167$; Alzheimer’s disease, $P = 0.247$). Similarly, the overall main effect for Condition persisted [$F(1,36) = 9.643, P = 0.004$] with performance in the Physical condition remaining significantly higher than performance in the ToM condition, irrespective of group ($P < 0.0001$).

Finally, the Group × Condition interaction remained highly significant [$F(3,36) = 20.832, P < 0.0001$]. Sidak post hoc tests confirmed that patients with behavioural variant FTD were significantly impaired in the Physical condition ($P = 0.015$) whereas patients with semantic dementia and Alzheimer’s disease scored in line with control subjects (semantic dementia, $P = 1.000$; Alzheimer’s disease, $P = 0.435$). On the ToM subscale, however, both semantic dementia and behavioural variant FTD patients showed significant impairments relative to control subjects (semantic dementia, $P = 0.003$; behavioural variant FTD, $P < 0.0001$) with patients with Alzheimer’s disease scoring at control levels ($P = 0.291$). No significant differences were evident between patients with semantic dementia and behavioural variant

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Table 2 Performance on the Physical and ToM subscales of the Cartoons task by participant group (standard deviation)

<table>
<thead>
<tr>
<th>Cartoons Task Subscale</th>
<th>Semantic dementia</th>
<th>Behavioural variant FTD</th>
<th>Alzheimer’s disease</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 11)</td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>Physical (10)</td>
<td>5.9 (2.5)</td>
<td>6.7 (1.3)</td>
<td>7.8 (1.0)</td>
<td>9.6 (0.6)</td>
</tr>
<tr>
<td>ToM (10)</td>
<td>4.0 (1.5)</td>
<td>3.0 (1.6)</td>
<td>7.0 (1.6)</td>
<td>8.5 (0.9)</td>
</tr>
</tbody>
</table>

*Maximum score for each subscale in brackets.

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![Figure 1](image_url)
FTD for ToM performance ($P = 0.313$). Analysing performance within the groups, Alzheimer's disease and control participants showed equivalent performance across conditions (Alzheimer's disease, $P = 0.486$; control subjects, $P = 0.924$), whereas performance on the ToM subscale was disproportionately affected in the semantic dementia ($P < 0.0001$) and behavioural variant FTD ($P < 0.0001$) groups.

Voxel-based morphometry analyses

**Patterns of atrophy**

Figure 3 illustrates the patterns of brain atrophy displayed by each patient group in comparison to healthy control participants using the threshold free cluster enhancing method (tfce) and corrected for family-wise error (FWE) at $P < 0.005$ with a cluster threshold of 300 contiguous voxels. Patients with semantic dementia showed temporal lobe atrophy bilaterally, including the temporal fusiform cortices, temporal poles, parahippocampal gyri, hippocampi, amygdalae, insular cortices and lateral temporal cortices. This profile of atrophy was more pronounced in the left than the right hemisphere extending into the orbitofrontal cortex and frontal pole. The behavioural variant FTD group showed extensive atrophy bilaterally, more pronounced in the right than the left hemisphere, in frontal and temporal regions including the orbitofrontal and medial prefrontal cortices, the frontal poles as well as the temporal fusiform cortex, temporal poles, hippocampi, amygdalae, and insular cortices. Finally, the Alzheimer's disease group demonstrated atrophy in a distributed set of regions including the bilateral hippocampi and parahippocampal gyri, bilateral temporal fusiform cortices, and left frontal lobe. These overall patterns of atrophy are consistent with previous reports in the literature for semantic dementia (Mion et al., 2010), behavioural variant FTD (Rosen et al., 2002), and Alzheimer's disease (Karas et al., 2004) (Table 4 and Fig. 3).

Direct comparison of the semantic dementia and patients with behavioural variant FTD revealed significantly greater atrophy in
the left temporal lobe, including the left lateral temporal cortices, left temporal pole, left parahippocampal gyrus, left amygdala, left hippocampus, and left insular cortex in the semantic dementia group. The reverse contrast failed to reveal any significant clusters at the $P < 0.005$ threshold (Supplementary Fig. 1).

**Neural correlates of theory of mind performance**

In keeping with our behavioural analyses, we included Comprehension performance as a covariate in the VBM analyses to control for possible semantic processing influences on this task. Age was also included as a nuisance variable in these analyses. We constrained our focus to the behavioural variant FTD and semantic dementia patient groups, given that significant alterations in ToM processing were not found in the Alzheimer’s disease group. Using a voxel-wise approach, with $P < 0.001$ uncorrected and a cluster threshold of 300 contiguous voxels, ToM deficits in patients with semantic dementia were related to grey matter intensity decrease in the right temporal fusiform cortex, and right inferior temporal gyrus, as well as the temporal poles and amygdala bilaterally. Further regions implicated in the semantic dementia group included the left orbitofrontal cortex, and the left insular cortex (Table 5 and Fig. 4).

ToM performance in patients with behavioural variant FTD was strongly associated with grey matter intensity decrease in right lateral temporal and right prefrontal regions including the right temporal fusiform cortex, right temporal pole, right hippocampus, right amygdala, and right thalamus as well as the right orbitofrontal cortex and medial prefrontal cortex. The integrity of the left insular and orbitofrontal cortices was also implicated in ToM performance in the behavioural variant FTD group (Table 5 and Fig. 4).

**Discussion**

This study is the first to investigate the neural substrates of theory of mind (ToM) impairments in semantic dementia in contrast with the behavioural variant FTD and Alzheimer’s disease. Using a simple cartoons task, we demonstrated significant ToM impairments in semantic dementia and behavioural variant FTD, with no significant deficits evident between Alzheimer’s disease and control subjects for ToM processing. Importantly, ToM deficits persisted in semantic dementia when controlling for semantic comprehension, indicating that a global semantic disruption is not the sole mechanism underlying ToM impairments in this disorder. Neuroimaging analyses revealed that ToM deficits were strongly associated with atrophy in right anterior temporal lobe structures, suggesting that social cognitive deficits emerge in semantic dementia with encroachment of the pathological process into the right anterior temporal lobe.

The extent to which ToM capacity is disrupted in semantic dementia remains notably underexplored, despite mounting evidence of interpersonal difficulties and behavioural egocentrism in this patient group (Rankin et al., 2005; Duval et al., 2012;
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Table 5 Voxel-based morphometry results showing regions of grey matter intensity that covary with ToM performance in semantic dementia and behavioural variant FTD patient groups

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Regions</th>
<th>Side</th>
<th>Number of voxels</th>
<th>MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic dementia and control subjects</td>
<td>Temporal fusiform cortex, temporal pole, inferior temporal gyrus, amygdala</td>
<td>Right</td>
<td>2072</td>
<td>x:2 y:-4 z:-50</td>
</tr>
<tr>
<td></td>
<td>Temporal pole, amygdala, orbitofrontal cortex</td>
<td>Left</td>
<td>874</td>
<td>x:-26 y:18 z:-40</td>
</tr>
<tr>
<td></td>
<td>Insular cortex</td>
<td>Left</td>
<td>493</td>
<td>x:-26 y:24 z:-2</td>
</tr>
<tr>
<td></td>
<td>Temporal fusiform cortex, temporal pole, amygdala, caudate, orbitofrontal cortex, medial prefrontal cortex, frontal pole</td>
<td>Right</td>
<td>1631</td>
<td>x:38 y:-4 z:-40</td>
</tr>
<tr>
<td></td>
<td>Insular cortex, frontal operculum cortex</td>
<td>Left</td>
<td>652</td>
<td>x:-36 y:14 z:2</td>
</tr>
<tr>
<td></td>
<td>Orbitofrontal cortex</td>
<td>Left</td>
<td>381</td>
<td>x:-14 y:26 z:-28</td>
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<tr>
<td></td>
<td>Hippocampus, thalamus</td>
<td>Right</td>
<td>326</td>
<td>x:26 y:-22 z:-16</td>
</tr>
</tbody>
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All clusters reported using voxel-wise contrasts and uncorrected at P < 0.001. Age and Comprehension performance included as a covariate in all contrasts. All clusters reported at t > 4.24 with a cluster threshold of 300 contiguous voxels.

Figure 4 Voxel-based morphometry analyses showing brain regions in which grey matter intensity correlates significantly with theory of mind performance in (A) semantic dementia and Control participants (MNI coordinates: x = 40, y = 2, z = −40), and (B) behavioural variant FTD and Control participants (MNI coordinates: x = 4, y = 8, z = −18). Coloured voxels show regions that were significant in the covariate analyses with P < 0.001 uncorrected with a cluster threshold of 300 contiguous voxels. All clusters reported t > 4.24. Clusters are overlaid on the MNI standard brain. L = left.

Irish et al., 2013). Our findings of severe ToM impairments in a sample of patients with left predominant semantic dementia, characterized by a primary deficit in semantic processing, corroborate a previous report of marked deficits across cognitive and affective aspects of ToM in left semantic dementia (Duval et al., 2012). Duval et al. (2012) noted that semantic dementia patients displayed a tendency to justify their ToM responses based on their own preferences, reinforcing the observation of an egocentric world view in this patient group (Snowden et al., 2001). Our findings support the existence of ToM deficits in semantic dementia, but argue against the view that semantic memory impairments are the sole mechanism by which such social cognitive deficits emerge. Using a scoring system to avoid overly penalizing patients with semantic dementia for their severe anomia, significant ToM impairments persisted in our semantic dementia group even when covarying for semantic processing deficits. This finding supports the suggestion that disrupted semantic processing does not fully account for social cognitive deficits in semantic dementia (Duval et al., 2012).

Neuroimaging analyses implicated a network of brain structures that seem critical for successful ToM performance in semantic dementia, including the right temporal fusiform cortex, right inferior temporal gyrus, bilateral temporal poles, and bilateral amygdalae, as well as the left orbitofrontal cortex and left insular cortex. The emergence of predominantly right-sided structures in a well-characterized cohort of patients with left-lateralized semantic dementia likely reflects the encroachment of the pathological process into the contralateral hemisphere with disease progression. It has been noted previously that the binary classification into left or right semantic dementia obscures the fact that a degree of bilateral atrophy is invariably present in these patients (Galton et al., 2001; Mion et al., 2010). Indeed, our voxel-based morphometry analyses revealed that although the left hemisphere was overwhelmingly affected in our semantic dementia group, bilateral insult to the amygdalae, anterior temporal cortices, and temporal poles was also present. It is likely therefore, that the extent to which social cognitive processes are disrupted in semantic dementia depends upon the integrity of right anterior temporal structures, with ToM impairments and behavioural egocentrism becoming more prominent with disease evolution (Thompson et al., 2003; Seeley et al., 2005). We have demonstrated here that cases with left predominant semantic dementia, in which atrophy has progressed to the contralateral hemisphere, present with marked disturbances in ToM processing, which in turn are corroborated by caregiver ratings of severe alterations in cognitive and emotional aspects of everyday interpersonal functioning on the Interpersonal Reactivity Index. These findings are also very much in keeping with previous clinical reports of more striking personality and social changes in those semantic dementia cases presenting with predominantly right temporal lobe pathology...
Although it has been proposed that left hemisphere hypometabolism accounts for compromised ToM performance in semantic dementia (Duvall et al., 2012), our results suggest that insult to right anterior temporal lobe structures is pivotal in the genesis of ToM dysfunction over and above semantic processing impairments arising from left temporal lobe atrophy.

Turning to the behavioural variant FTD group, our findings of significant ToM impairments resonate with reports of gross interpersonal and socioemotional disturbances in this syndrome (Snowden et al., 2003; Torralva et al., 2007; Kumfor et al., 2011). The mechanisms underlying the disruption of ToM in behavioural variant FTD remain poorly understood. It has been suggested that executive dysfunction represents a key mechanism underlying the capacity for cognitive ToM (Poletti et al., 2012); however, few studies have investigated and found evidence for a significant association between cognitive ToM impairments and executive dysfunction in behavioural variant FTD (Snowden et al., 2003; Eslinger et al., 2007). We did not find a significant association between the measures of executive functioning (Digit span backwards, Trail Making Test) and ToM performance in our behavioural variant FTD group. The proposed relationship between executive dysfunction and ToM is contentious (Roca et al., 2011) and may depend on the nature of the task used to assess ToM and the severity of the patient samples (Fernandez-Duque et al., 2009). Consideration of the role of inhibitory processes represents a line of potential importance in this regard, particularly in light of the profound disruption to inhibitory control processes typically seen in behavioural variant FTD (Hornberger et al., 2011). A recent study has suggested that ToM disruption in behavioural variant FTD may in fact reflect an inability to inhibit one’s own perspective, which in turn has been shown to correlate significantly with hypometabolism in the right lateral prefrontal cortex (Le Bouc et al., 2012). Although distinctive interpersonal and personality changes have been found to correlate with frontal lobe integrity in behavioural variant FTD (Rankin et al., 2003; Sollberger et al., 2009), our neuroimaging findings accord well with a growing body of evidence implicating right-sided anterior temporal lobe degeneration across social cognitive and affiliative trait disruption in this syndrome (Edwards-Lee et al., 1997; Rankin et al., 2003; Eslinger et al., 2007; Kipps et al., 2009; Sollberger et al., 2009).

The social brain

Using a combination of experimental tasks in two FTD clinical phenotypes, we have elucidated a set of distinct regions in the frontal and anterior temporal lobes that may be specialized for sophisticated acts of social inference. These brain regions are core structures in a brain network commonly referred to as the ‘social brain’ (Brothers, 1990; Frith, 2007). Much of the research focus to date, however, has concentrated on the putative roles of the amygdala and prefrontal cortex in mediating social and emotional processing with relatively less information available regarding the potential role of the anterior temporal lobe (Wong and Gallate, 2012). A recent study in temporal lobe epilepsy has argued against the involvement of lateral temporal regions in ToM processing (Giovagnoli et al., 2011). Importantly, however, the lesions in the temporal lobe epilepsy group were predominantly in the superior rather than anterior lateral temporal regions. Our results offer novel lesion study evidence in favour of a pivotal role for the anterior temporal lobes in the attribution of mental states of others. The results presented here complement the functional MRI literature in which the anterior temporal lobes have been observed to activate on tasks with socially relevant content such as moral reasoning (Zahn et al., 2009b) and ToM performance (Gallagher and Frith, 2003). The involvement of the right anterior temporal lobe in ToM performance accords well with the suggestion that this brain region is particularly sensitive to stimuli that convey socially important narratives and to tasks which require interpretation of others’ emotions, intentions, or beliefs (Olson et al., 2007). Although the left anterior temporal lobe is classically associated with the processing of semantic and conceptual knowledge (Mion et al., 2010; Visser et al., 2010), the right temporal pole has been posited to play an integral role in the linking of sensory representations with emotional responses and social memory (Olson et al., 2007), and the preferential processing of socially relevant concepts (Simmons and Martin, 2009; Wong and Gallate, 2012). Our finding of a significant relation between pronounced alterations in ToM processing in semantic dementia and primarily right anterior temporal lobe structure pathology therefore underscores the putative specialization of the right anterior temporal lobe for mediating complex socioemotional functions.

A number of points need to be considered with regards to our results. First, it has been suggested that specific subregions within the anterior temporal lobes may preferentially code for social versus non-social entities (Olson et al., 2013). Given the widespread neural degeneration evident in semantic dementia and behavioural variant FTD, it was not possible to determine the functional specialization of anterior temporal lobe subregions for specific aspects of ToM. Second, the neuroimaging covariate results were reported uncorrected at P < 0.001, as they did not survive conservative corrections for multiple comparisons. Importantly, we reduced the potential for false positive results in these covariate analyses by applying stringent cluster extent thresholds of 300 contiguous voxels. This cluster thresholding approach has been demonstrated to be an effective tool to reduce the risk of false positive findings without compromising the statistical power of the study (Forman et al., 1995) and thus allows us confidence in our findings. Third, given the recent shift in perspective from brain structures in isolation to the study of neural networks, it will also be important for future work to elucidate how alterations in structural connectivity across dementia syndromes impinge upon the capacity for ToM attribution. Future studies incorporating semantic dementia samples at varying stages of the disease trajectory and measures of structural connectivity will be helpful in replicating and expanding upon our current results. Finally, ToM performance has been fractionated into cognitive and affective components, with these subcomponents ascribed to distinct neuroanatomical networks (Poletti et al., 2012, but see Pessoa, 2008). The cartoons task used in this context probed cognitive and affective aspects of ToM in parallel and did not permit the dissociation between these two aspects of social cognition. It is
notable, however, that our neuroimaging analyses revealed significant involvement of limbic and anterior cortical regions including the amygdala, temporal pole, orbitofrontal cortex and ventromedial prefrontal cortex, suggesting that the task stresses affective as well as cognitive aspects of ToM reasoning. Further work will be necessary to tease apart the extent to which cognitive and affective components of ToM are compromised in neurodegenerative disorders and the specific neural regions that are recruited for these aspects of ToM processing. We suggest that the development of experimental tasks which differentially stress prefrontal versus anterior temporal aspects of social cognitive functioning in FTD syndromes will prove particularly illuminating in this regard.

From a clinical perspective, our results offer important insights into the social and behavioural changes that emerge during the semantic dementia disease course. The syndrome of semantic dementia is typically conceptualized in terms of cognitive and language dysfunction. Indeed, the promotion of the term semantic variant primary progressive aphasia (Gorno-Tempi et al., 2011) to describe semantic dementia emphasizes this position. The majority of these patients, however, show parallel behavioural disturbances and alterations in the capacity to mentalize, changes that may produce greater carer distress than the core cognitive deficits (Hsieh et al., 2013). Our study points to the marked disruption of socioemotional processing in semantic dementia, which cannot be understood purely in terms of a primary semantic impairment. It remains unknown at what stage in the semantic dementia pathological process such social cognitive deficits manifest. Correlation analyses failed to reveal a significant relationship between ToM deficits and measures of disease duration in the current semantic dementia sample. This lack of association, however, is not surprising, given the disease stage of our patients. As such, it will be important for future studies to recruit relatively mild cases of semantic dementia with circumscribed left anterior temporal lobe atrophy to chart the evolution of ToM deficits and their relation to anterior temporal lobe degeneration over time. Such prospective approaches will serve to improve the characterization of non-language features of the semantic dementia syndrome, their relationship to behavioural symptoms and disease progression, as well as the resultant real life impact of such disturbances.

In summary, this study represents the first direct investigation of the neural substrates of ToM deficits in left dominant semantic dementia, in contrast with behavioural variant FTD. Our results reveal significant alterations in ToM performance in semantic dementia, not exclusively attributable to semantic processing impairments, which correlate with atrophy in a discrete set of predominantly right-lateralized anterior temporal brain structures. Our findings underscore the pivotal role of the anterior temporal lobes in the successful inference and attribution of mental states of others, and point towards a crucial role for the right anterior temporal lobe in complex social cognitive processes. Taken together, these findings highlight the marked disruption of cognitive functions beyond the language domain in semantic dementia and provide novel insights for our understanding of the brain regions crucial for successful social functioning in everyday life.

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Supplementary material

Supplementary material is available at Brain online.

References


