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Michel, Caroline ; Dricot, Laurence ; Lhommel, Renaud ; Grandin, Cécile ; Ivanoiu, Adrian ; et al. *Extensive left temporal pole damage does not impact on Theory of Mind abilities*. In: *Journal of Cognitive Neuroscience*, Vol. 25, no.12, p. 2025-2046 (2013)

DOI : 10.1162/jocn_a_00488

Extensive Left Temporal Pole Damage Does Not Impact on Theory of Mind Abilities

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Abstract

■ The temporal poles (TPs) are among the brain regions that are often considered as the brain network sustaining our ability to understand other people's mental states or "Theory of Mind" (ToM). However, so far the functional role of the left and right TPs in ToM is still debated, and it is even not clear yet whether these regions are necessary for ToM. In this study, we tested whether the left TP is necessary for ToM by assessing the mentalizing abilities of a patient (C.M.) diagnosed with semantic dementia. Converging evidence from detailed MRI and ^{18}F-fluoro-2-deoxy-D-glucose PET examinations showed a massive atrophy of the left TP with the right TP being relatively unaffected. Furthermore, C.M.'s atrophy encompassed most regions of the left TP usually activated in neuroimaging studies investigating ToM. Given C.M.'s language impairments, we used a battery of entirely nonverbal ToM tasks. Across five tasks encompassing 100 trials, which probed the patient's ability to attribute various mental states (intentions, knowledge, and beliefs), C.M. showed a totally spared performance. This finding suggests that, despite its consistently observed activation in neuroimaging studies involving ToM tasks, the left TP is not necessary for ToM reasoning, at least in nonverbal conditions and as long as its right counterpart is preserved. Implications for understanding the social abilities of patients with semantic dementia are discussed. ■

INTRODUCTION

A key aspect of human social cognition is the ability to understand other people's mental states (their intentions, knowledge, beliefs, and emotions), an ability referred to as having or using a "Theory of Mind" (ToM; Premack & Woodruff, 1978). Neuroimaging studies suggest that this ability recruits a large brain network including the medial pFC, the TPJ bilaterally, the anterior paracingulate cortex, and the left and right temporal poles (TPs; e.g., Carrington & Bailey, 2009; Van Overwalle, 2009; Brüne & Brüne-Cohrs, 2006; Frith & Frith, 2003, 2006; Gallagher & Frith, 2003; see also Olson, Plotzker, & Ezzyat, 2007). However, to date, the functional role of these regions in ToM is still debated. Most importantly, it is not clear whether all these regions are necessary for ToM. Most research aiming at addressing this issue has focused on the pFC and the TPJ (e.g., Samson, Apperly, & Humphreys, 2007; Bird, Castelli, Malik, Frith, & Husain, 2004; Samson, Apperly, Chiavarino, & Humphreys, 2004; Rowe, Bullock, Polkey, & Morris, 2001; Stuss, Gallup, & Alexander, 2001). In the current study, we focused on the TPs.

Two main hypotheses have been put forward regarding the functional role played by the TPs in ToM. According to the first hypothesis, the TPs would provide access to autobiographical memories, that is, one's own past experiences, including the mental states involved in these experiences (e.g., Moriguchi et al., 2006; Frith & Frith, 2003; Gallagher & Frith, 2003). According to the second hypothesis, the TPs' activation during ToM tasks would reflect the access to semantic information. Some authors have construed this semantic information as "social script knowledge" (Frith & Frith, 2003; Gallagher & Frith, 2003), that is, knowledge about the generic goals and activities associated with specific social situations, whereas others have construed it as "social concepts" (e.g., Skipper, Ross, & Olson, 2011; Ross & Olson, 2010; Simmons, Reddish, Bellgowan, & Martin, 2010; Zahn et al., 2007, 2009), that is, abstract representations of psychological states that enable us to describe social agents' behavior (Zahn et al., 2007, 2009). So far, however, no evidence clearly favors one hypothesis over the other, and there seems to be inconsistencies regarding the involvement of the right versus the left TP in these putative functions.

Besides the question of the functional role of the TPs in ToM, a more fundamental issue that has not been clarified yet is whether the involvement of the TPs in ToM is necessary at all. For example, it could be that the activation of the TPs in ToM tasks simply reflects processes

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Journal of Cognitive Neuroscience 25:12, pp. 2025–2046
doi:10.1162/jocn_a_00488

that are prompted by but are not necessary for ToM reasoning. Furthermore, if reasoning about other people's mental states does require the TP's contribution, does it require one of the TPs only or both?

Whether or not the left and/or right TPs are necessary for ToM can be directly addressed in lesion studies investigating how damage to these regions affects ToM abilities. Several populations of patients seem particularly relevant for this investigation: patients who have undergone neurosurgery targeted at the anterior temporal lobe (aTL), patients suffering from HSE, a pathology associated with pathological tissue in the TPs (e.g., Kapur et al., 1994), and patients suffering from the temporal variant of frontotemporal dementia or "semantic dementia," a pathology associated with brain atrophy most pronounced in the TPs (e.g., Studholme et al., 2004; Mummery et al., 2000). There is evidence that some of these patients who have bilateral damage show significant changes in their social behavior (e.g., in cases of aTL resection: Terzian & Ore, 1955; in cases of HSE: Lilly, Cummings, Benson, & Frankel, 1983; in cases of semantic dementia: Rankin et al., 2006; Snowden et al., 2001; Bozeat, Gregory, Lambon Ralph, & Hodges, 2000; Edwards-Lee et al., 1997) and are impaired on formal assessments of ToM (Duval et al., 2012; Rankin et al., 2009; patients with semantic dementia in both cases). However, given that the lesions were bilateral and that they also extended to other areas than the TPs, it is difficult to ascertain that damage to the TPs played a causal role in the ToM impairment and if so, whether it concerned the left TP, the right TP, or both TPs. The evidence from patients with unilateral damage to the TP areas does not clarify the picture either. Ghika-Schmid, Assal, De Tribolet, and Regli (1995) reported significant changes in social behavior in a patient who had undergone left temporal lobectomy. Stone, Baron-Cohen, Calder, Keane, and Young (2003) reported difficulties in two ToM tasks in a patient suffering from HSE (patient S.E.) who had bilateral lesions to the amygdala but whose lesions seemed to only affect the right TP. In contrast, preserved ToM abilities have been reported in patients who had a unilateral (left or right) aTL resection (Shaw et al., 2004, 2007). The conclusions that can be drawn from these studies is limited by the fact that the patients reported by Stone et al. (2003) and Ghika-Schmid et al. (1995) had also lesions to other areas than the TPs and that, in the studies by Shaw et al. (2004, 2007), the extent to which the TP was affected by the surgery is not reported in detail (it was not the scope of these studies).

Thus overall, with the evidence available so far, it remains unknown whether or not the left and/or right TPs are necessary for ToM. All scenarios are still possible. It might be that neither the left nor the right TP are necessary for ToM. In this first case, damage to the left and/or right TP(s) would not lead to ToM impairment. The impairments in ToM tasks (and changes in social behavior, if these changes did reflect a ToM impairment) observed in patients with a pathology affecting the TP(s) would be because of brain damage extending beyond the TPs. It is also possible that only one of the TPs is necessary for ToM, either the left TP (second scenario) or the right TP (third scenario). In these two cases, a ToM impairment would be observed only if the critical TP is affected and obviously following bilateral TP damage. The left and right TPs might also be each necessary for ToM. In this fourth case, a ToM impairment would be observed following damage to the left or right TP. Finally, only one of the TPs, irrespective as to whether it is the left or the right one, may be necessary for ToM (for a similar proposal, see the hypothesis of a redundant role of the left and right aTLs in general semantic processing, put forward by Lambon Ralph, Ehsan, Baker, & Rogers, 2012; Lambon Ralph, Cipolotti, Manes, & Patterson, 2010; Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001). In that fifth case, normal functioning of one of the TPs would be necessary and sufficient for successful ToM reasoning. ToM impairment would be observed when both the left and right TPs are affected. Separating out these various scenarios requires a systematic investigation of the consequences of well-documented unilateral damage to the left TP and to the right TP on ToM reasoning. In the current study, we provide one piece of this puzzle by examining the impact of a massive and markedly asymmetric atrophy to the left TP on ToM in a patient (C.M.) diagnosed with semantic dementia. Importantly, because the patient's semantic deficit was associated with nonsemantic language impairments (as commonly observed in semantic dementia; see, e.g., Patterson et al., 2006), we used a battery of entirely nonverbal ToM tasks.

CASE REPORT

C.M. is a right-handed man who presented to the Cliniques Universitaires Saint-Luc, Brussels, in May 2007, with complaints of progressive language production and comprehension difficulties. At that time, aged 56, the patient had just stopped working as a manager of a small textile company, as a consequence of the closing down of the company. C.M. started to work at the age of 14 after 8 years of formal education, and he took evening classes in electronics for 7 years. The patient had also served as a pastor in his town for 10 years, a function that he had to progressively give up because of his language deficits.

The first neuropsychological and language examination carried out in May 2007 showed deficits both in word production and word comprehension tasks in the context of a fluent spontaneous speech, with all other aspects of cognitive functioning being preserved. Two years later (May 2009), the neuropsychological assessment showed a further deterioration of language functions whereas cognitive functioning still remained well preserved (see Tables 1 and 2). The MRI scan performed in 2007 and 2009 (see technical details below) showed an atrophy of the left frontotemporal region. On the basis of all these elements and in agreement with what has been described in the literature

(see Garrard & Hodges, 2000) as well as with the diagnostic criteria established by McKhann et al. (2001) and Neary et al. (1998), C.M. was diagnosed with semantic dementia.

The formal investigation of C.M.'s ToM reasoning abilities was carried out between February and October 2011, in parallel with a detailed neuroanatomical investigation of the patient's brain damage and an investigation of his behavior in daily life. At that time, the patient's language and semantic processing was also reexamined in detail (see Table 2). C.M.'s performance was severely impaired in verbal comprehension tasks, suggesting a semantic deficit. However, as already observed in 2009, the patient's linguistic abilities were also impaired beyond the semantic deficit. Indeed, C.M.'s performance was severely impaired in auditory and written lexical decision tasks (where he was asked to discriminate between words and pseudowords), revealing a presemantic deficit in the ability to recognize spoken and written words. A postsemantic deficit was also suspected, based on the patient's errors in spoken naming. He produced phonemic paraphasias and sometimes produced the expected spoken word but with a regularization error, suggesting that he resorted to his orthographical lexical knowledge to produce the phonological output that he was not able to access directly. Nonverbal visual processing seemed to be spared as evidenced by a perfect performance on an object/nonobject decision task (see Table 2). Given C.M.'s verbal pre- and postsemantic deficits but his spared visual processing, the extent of the semantic deficit was best reflected in entirely nonverbal semantic tasks such as the picture versions of the "Pyramid and Palm Trees Test" (Howard & Patterson, 1992) and the "Kissing and Dancing Test" (Bak & Hodges, 2003) assessing conceptual knowledge about concrete objects and actions, respectively. On the Kissing and Dancing Test, C.M.'s performance was within the controls' range of performance. On the Pyramid and Palm Trees Test, his performance was significantly impaired although to a much lesser extent than his performance on the verbal version of the same task. Such a pattern characterized by semantic and additional presemantic/postsemantic deficits is not uncommon in semantic dementia patients (see, e.g., Patterson et al., 2006; see also Lambon Ralph et al., 2001) and might be accounted for by the patient's extended atrophy in the left hemisphere (see neuroanatomical details below). In any case, C.M.'s pattern clearly motivated the use of nonverbal ToM tasks as the only reliable means to assess the patient's ToM abilities.

The research protocol was approved by the biomedical ethic committee of the Cliniques Universitaires Saint-Luc (Brussels), and the patient and his spouse gave their written informed consent.

NEUROANATOMICAL INVESTIGATION

In 2007, 2009, and 2011, MRI data were acquired with Fluid Attenuated Inversion Recovery (FLAIR) images being obtained in the axial plane. In addition, axial T2*-weighted images were acquired in 2009 and 2011, whereas axial diffusion weighted images and coronal T2-weighted images were acquired in 2007 and 2009. The examination in 2011 was performed on a 3T scanner (Achieva, Philips Healthcare, Eindhoven, The Netherlands) with a 32-channel phased-array head coil, and 3-D heavily T1-weighted images were also recorded. The anatomical 3-D sequence consisted in a gradient-echo sequence with an inversion prepulse (Turbo Field Echo) acquired in the sagittal plane using the following parameters: repetition time /echo time/flip angle = 9.1 msec/4.6 msec/8°, 150 slices, slice thickness = 1 mm, in-plane resolution = 0.81×0.95 mm^2 (acquisition) reconstructed in 0.75×0.75 mm^2, field of view = 237×197 mm^2, acquisition matrix = 296×251 (reconstruction 320^2), SENSE factor = 1.5 (parallel imaging).

An experienced neuroradiologist described a left hemispheric atrophy encompassing mainly the temporal and part of the frontal lobes, which was already present in 2007 and worsening progressively with time. The whole left temporal lobe was severely atrophic with an anterior predominancy. The left amygdala was also severely atrophic, and the left hippocampus was atrophic mainly in its middle and middle-posterior segments. The left inferior frontal gyrus was clearly atrophic around the sylvian fissure (Broca area) as well as the posterior part of the left middle frontal gyrus (premotor area). A moderate atrophy of the left supramarginal and angular gyri was also noted. On the right side, a slight atrophy of the TP became visible in 2011. No other lesion was noted, and the patient had no vascular ischemic lesion (leucoaraiosis rated as 2/9 according to the scale of Manolio; Longstreth et al., 1996; Manolio et al., 1994).

Volume- and surface-based analyses (FreeSurfer; Martinos Center for Biomedical Imaging, Boston, MA, USA) comparing the patient with an independent sample of 29 healthy adults (15 men, 14 women; mean age = 61.4 years, *SD* = 6.6 years) were also performed. The whole brain was segmented by completing the FreeSurfer image analysis pipeline, which is documented and freely available for download on-line (http://surfer.nmr.mgh.harvard.edu/). The final segmentation is based on both a subject-independent probabilistic atlas and subject-specific measured values. The atlas is built from a training set, that is, a set of 40 participants whose brains (surfaces or volumes) have been labeled by hand (only 10 participants for the Brodmann's areas). The technical details of these procedures were described in prior publications (Fischl et al., 2002, 2004; Ségonne et al., 2004; Dale, Fischl, & Sereno, 1999).

The volumetric analyses (see Table 3) revealed a significant white matter reduction in the left TP as well as in the left enthorinal cortex and fusiform gyrus. A significant atrophy was also revealed in the left hippocampus (particularly in the fimbria, the presubiulum, and the subiculum) as well as in the left amygdala and accumbens area. A widening of the inferior lateral ventricles was also demonstrated bilaterally, although much larger on the left side.

Table 1. C.M.'s Neuropsychological Profile in 2007 and 2009

	May 2007		*May 2009*	
Test	*C.M.'s Performance*	*Percentile (P) or SD*	*C.M.'s Performance*	*Percentile (P) or SD*
Attention				
D2 cancellation task[a]				
Speed	367	*P* 50	263	*P* 9.7
Quality	5.7%	*P* 50–*P* 75	1.9%	>*P* 90
Profitability	346	*P* 57.9	258	*P* 18.4
Regularity	11	*P* 50–*P* 75	6	>*P* 90
Long-term Memory				
Visual				
Doors Test[b]				
Part A	12/12	≥*P* 75	12/12	≥*P* 75
Part B	10/12	*P* 90	9/12	*P* 75
Total	22/24	*P* 90	21/24	*P* 75–*P* 90
Verbal				
Buschke 15 items[c]				
Mean	8	<*P* 1	4.7	<*P* 1
List learning	47.5%	*P* 5–*P* 50	0%	<*P* 1
Delayed free recall	7	*P* 1–*P* 5	5	<*P* 1
Recognition	14	Pathological	n.t.	/
Executive Functions				
Trail Making Test[d]				
Part A, time (s)	37	*P* 25–*P* 50	34	*P* 25–*P* 50
Part A, errors	0	*P* 10–*P* 95	0	*P* 10–*P* 95
Part B, time (s)	105	*P* 10–*P* 25	79	*P* 25–*P* 50
Part B, errors	1	*P* 5	0	*P* 10–*P* 95
Fluency				
Category fluency (animals)	20	Level 1: −1.78 *SD*	11	Level 1: −3.64 *SD*
		Level 2: −1.69 *SD*		Level 2: −2.80 *SD*
Letter fluency (P)	18	Level 1: −0.43 *SD*	8	Level 1: −2.48 *SD*
		Level 2: −0.95 *SD*		Level 2: −2.22 *SD*
Luria's graphic series[e]	28/32	>pathological treshold (21.5)	30/32	>pathological treshold (21.5)
Constructive Praxis				
Cerad figures[f]				
Circle	1/2	n.a.	2/2	n.a.
Diamond	2/3	n.a.	3/3	n.a.

Table 1. (*continued*)

Test	May 2007		May 2009	
	C.M.'s Performance	*Percentile (P) or SD*	*C.M.'s Performance*	*Percentile (P) or SD*
Entangled rectangles	2/2	n.a.	2/2	n.a.
Cube	4/4	n.a.	3/4	n.a.
Total	9/11	−1.4 *SD*	10/11	−0.33 *SD*
Number Processing				
Simple mental arithmetical task	10/10	n.a.	9/10	n.a.
Written arithmetical task	3/5	n.a.	4/5	n.a.
Counting aloud (by 1 and 3 until *n*)	perfect	n.a.	perfect	n.a.

n.a. = not available; n.t. = not tested.

[a]Brickenkamp (1981).

[b]Baddeley, Emslie, and Nimmo-Smith (1994).

[c]Van der Linden et al. (2004).

[d]Reitan and Wolfson (1985).

[e]Luria (1980).

[f]Morris et al. (1989).

The surface-based analyses (see Table 3) revealed a significantly reduced mean cortical thickness only in the left hemisphere. On this side, the TP was again among the main regions characterized by a significantly reduced cortical thickness in C.M. compared with the control subjects. The atrophy encompassed the entire left temporal lobe, extending to the occipitotemporal cortex. The inferior frontal gyrus was also involved, with a significant reduced cortical thickness in the opercular and triangular parts, including Brodmann's area 44 (Broca area). A reduced cortical thickness was also observed in the left supramarginal and angular gyri. The right hemisphere was relatively preserved. Regarding the right TP, a significant difference (although smaller than in the left hemisphere) between C.M. and the control subjects was only observed in the polar part of the superior temporal gyrus. (See Table 3 for a complete listing of the brain regions showing a significantly different cortical thickness in C.M.)

To estimate the impact of the underlying disease on the regional brain metabolism, the patient also underwent a brain PET/CT study on a Philips 16 GEMINI TF camera (Philips Healthcare, The Netherlands), 38 min after intravenous injection of 152 MBq of ^{18}F-fluoro-2-deoxy-D-glucose (FDG). The FDG PET acquisition was coregistred with the 3-D T1-weighted turbo field echo MRI for visual interpretation (Figure 1A). Automated voxel-based analysis was also computed using PBRAIN_3.308 software (PMOD Technologies Ltd., Zurich) by comparing the patient to an on-site normal database composed of 32 healthy participants (16 men) aged between 60 and 80 years (mean age = 70.8 years, *SD* = 6.2 years). After spatial normalization into the Montreal Neurological Institute space (human normalization templates derived from SPM5, www.fil.ion.ucl.ac.uk/spm/software/spm5/), the PET FDG acquisition was smoothed with a Gaussian 8-mm filter, and individual voxel values were normalized to a predefined cerebellar region of reference. Automatic *z*-scores map distribution, superimposed to the FDG distribution (Figure 1B), was then generated based on the pooled variance analysis protocole. Two different sets of VOIs atlas (Human AAL Brain Template VOIS, Tzourio-Mazoyer et al., 2002; HA n30r83 Template VOIs, Hammers et al., 2003) were then applied to the normalized FDG study to obtain regional statistics of the *z*-scoring distribution. Most representative deficits of regional FDG uptakes, corresponding to negative *z* scores < -1.3, are listed in Table 4. These deficits roughly overlapped the reduced white matter reduction and the reduced cortical thickness (see volume- and surface-based analyses). On the left side, the entire temporal lobe was concerned, including the superior, middle, and inferior temporal gyri; the fusiform gyrus; and importantly the whole aTL, including the TP (superior and middle parts). On the right side, the temporal lobe was much more preserved: Only marginal foci of pathological voxels were identified in the middle part of the TP according to the AAL atlas and in the superior and inferolateral parts of the aTL according to the HA n30r83 atlas. Corresponding negative *z*-score values were also less important than those found in the left temporal lobe. 3-D volume rendering of the *z*-score deficits distribution was generated to illustrate the spatial connection between the different FDG uptake deficits, using either neurostat/

Table 2. Language and Semantic Examination of C.M. in 2007, 2009, and 2011

Test	*CM's Score (%) in 2007*	*CM's Score (%) in 2009*	*CM's Score (%) in 2011*	*Controls' Mean Score (%) and p Value of the Modified t Test and/or [Controls' Range]*
Presemantic Processing Tasks				
Auditory lexical decision task[a,b]	n.t.	111/128[a]	102/144[b]	[a]: 124.6/128 [122–127][un]; [b]: n.a.
Visual lexical decision task[c]	n.t.	101/120	n.t.	118/120 [116–119][un]
Object/nonobject decision task[d,e]	n.t.	123/128[d]	30/30[e]	[d]: 114.7 [106–124]; [e]: n.a.
Word Production Tasks				
Written picture-naming task of the *Lexis*[f]	n.t.	45/80	n.t.	63.6/80 [58–73]
Spoken picture-naming task of the *Lexis*[f]	59/80	38/80	21/80	74.2/80; all $p < .001$
Spoken picture-naming task of an "*Object/action battery*"[g]				
Animals	n.t.	n.t.	5/24	21.04/24[un]; $p < .001$
Vegetables	n.t.	n.t.	8/24	22.12/24[un]; $p < .001$
Artifacts	n.t.	n.t.	6/24	21.88/24[un]; $p < .001$
Actions	n.t.	n.t.	1/24	20.16/24[un]; $p < .001$
Spoken picture-naming task of the "*Living/nonliving battery*"[h]				
Living items	n.t.	19/36	11/36	32.5/36 [28–36]
Nonliving items	n.t.	19/36	17/36	30.5/36 [27–33]
Word Comprehension Tasks				
Spoken word–picture matching task of the *Lexis*[f]	73/80	63/80	48/80	79.4/80; all $p < .001$
Spoken word–picture verification task of an "*Object/action battery*"[g]				
Animals	n.t.	n.t.	8/24	20.32/24[un]; $p < .001$
Vegetables	n.t.	n.t.	9/24	22.24/34[un]; $p < .001$
Artifacts	n.t.	n.t.	8/24	21.32/24[un]; $p < .001$
Actions	n.t.	n.t.	8/24	20.08/24[un]; $p < .001$
Spoken word–picture verification task of the "*Living/nonliving battery*"[h]				
Living items	n.t.	28/36	22/36	33.25/36 [30–35]
Nonliving items	n.t.	27/36	25/36	31.5/36 [28–34]
Synonym pointing task[i]				
Concrete nouns	n.t.	15/30	7/30	28.3/30 [27–29][un]
Abstract nouns	n.t.	18/30	7/30	28.3/30 [25–30][un]
Concrete verbs	n.t.	19/30	5/30	29.6/30 [29–30][un]
Abstract verbs	n.t.	19/30	14/30	28.3/30 [27–30][un]

Table 2. (*continued*)

Test	*CM's Score (%) in 2007*	*CM's Score (%) in 2009*	*CM's Score (%) in 2011*	*Controls' Mean Score (%) and p Value of the Modified t Test and/or [Controls' Range]*
Pyramid and Palm Trees Test words[j]	n.t.	43/52	28/52	50.67/52[un]; all $p < .001$
Kissing and Dancing Test words[k]	n.t.	45/52	31/52	51.5/52[un]; all $p < .001$
Nonverbal Semantic Tasks				
Pyramid and Palm Trees Test pictures[j]	n.t.	50/52	43/52	51.1/52; $p > .05$ in 2009; $p < .001$ in 2011
Kissing and Dancing Test pictures[k]	n.t.	48/52	48/52	50.4/52; $p > .05$
Reading Aloud Task[l]				
Words vs. nonwords	10/10 vs. 10/10	10/10 vs. 10/10	n.t.	n.a.
Regular vs. ambiguous vs. irregular words	6/6 vs. 5/6 vs. 5/6	6/6 vs. 4/6 vs. 2/6	n.t.	n.a.
Writing to Dictation Task[l]				
Regular vs. ambiguous vs. irregular words	4/4 vs. 2/4 vs. 2/4	4/4 vs. 2/4 vs. 2/4	n.t.	n.a.

n.a. = not available; n.t. = nontested; [un] = unpublished norms.

[a]Vidal and de Partz (unpublished).

[b]Described in Vannuscorps and Pillon (2011).

[c]de Partz (unpublished).

[d]Birmingham Object Recognition Battery (Riddoch & Humphreys, 1993).

[e]Reduced version of the object/nonobject decision task from Samson, Pillon, and De Wilde (1998).

[f]de Partz, Bilocq, De Wilde, Seron, and Pillon (2001).

[g]Vannuscorps and Pillon (unpublished).

[h]Samson et al. (1998).

[i]Pillon et al. (unpublished) described in d'Honincthun and Pillon (2008).

[j]Howard and Patterson (1992).

[k]Bak and Hodges (2003).

[l]Batterie d'évaluation du langage (Cliniques Universitaires Saint-Luc, Brussels).

3D-SSP software (D. Cross, S. Minoshima, Department of Radiology and Bioengineering, Washington National Primate Research Center, University of Washington, Seatlle, WA, USA; see Figure 1C) or 3D-volume rendering PMOD module (PMOD Technologies Ltd.; see Figure 1D).

Finally, to ensure that the left TP in which abnormalities were objectivized in C.M.'s brain did correspond to the brain region reported in ToM neuroimaging studies (see references in Table 5), we projected 31 foci of ToM activation observed in the TPs (or more widely in the aTLs) in neuroimaging studies onto C.M.'s anatomical data transformed into Talairach space (Talairach transformation; Talairach & Tournoux, 1988) as well as onto 13 control subjects' (men) anatomical data transformed into the same space (mean age = 59.31 years, range = 50–70 years, *SD* = 7.76 years), using BrainVoyager QX (Version 2.4.1.2052, Brain Innovation, Maastricht, The Netherlands; see Figure 2). The foci of ToM activation were reproduced by generating a spherical volume of 515 mm^3 (radius = 5 mm) around the Talairach coordinates reported in the neuroimaging studies. As detailed in Table 5, we observed a significant loss of (white and gray matter) volume in C.M., compared with the control subjects, in 13 of the 15 spheres projected on the left side, with 8 of 13 spheres being characterized by a loss of volume larger than 5 standard deviations (z scores mean = −7.48, range = −1.42 to −28.25, mean percentage of brain matter lost = 51.87%, range = 15.73–98.64%) and the loss of volume in the two other spheres approaching the significant level (z scores = −1.42 and −1.88 corresponding to a brain matter loss of 50.49% and 53.4%, respectively). It is worth noting that of the 15 spheres associated with ToM in the left TP, seven corresponded to foci of activation observed in nonverbal ToM tasks. Of these seven spheres, six showed a significant volume loss in C.M.

Table 3. List of Brain Regions for which the Volume (mm^3) or the Surface (mm) Was Significantly Different in C.M. Compared with 29 Healthy Participants

	C.M.	*Control Mean*	*Control SD*	*Z score*
Volumetric ROI				
Left inferior lateral ventricle	5186	665.79	393.86	11.48
Right inferior lateral ventricle	1732	600.45	334.16	3.39
Left fusiform gyrus-white matter	3692	6795.21	1165.94	−2.66
Left TP-white matter	349	729.24	141.49	−2.69
Left accumbens area	387	764.21	138.92	−2.72
Left enthorinal gyrus-white matter	254	951.79	247.90	−2.81
Left amygdala	565	1624.97	365.10	−2.90
Left hippocampus	1896	3846.72	570.12	−3.42
Fimbria	25	77.63	25.56	−2.06
Presubiculum	214	472.37	93.35	−2.77
Subiculum	251	625.12	121.32	−3.09
Surface ROI				
Mean thickness right	2.27	2.34	0.10	−0.67[a]
Mean thickness left	2.09	2.33	0.08	−2.77
Surface ROI in the left hemisphere				
Rectus gyrus	2.74	2.32	0.13	3.09
Suborbital sulcus	2.98	2.18	0.27	2.99
Calcarine sissure	1.57	1.81	0.13	−1.98
Inferior frontal gyrus-triangularis	2.01	2.32	0.16	−1.99
Posterior cingulate gyrus-dorsal	2.47	2.90	0.22	−2.00
Subcentral gyrus and sulcus	2.11	2.49	0.18	−2.12
Inferior frontal sulcus	1.70	2.00	0.13	−2.27
Postcentral sulcus	1.68	1.97	0.13	−2.28
Occipitotemporal lateral-fusiform gyrus	2.32	2.76	0.19	−2.28
Inferior circular insula sulcus	2.24	2.60	0.15	−2.46
Central sulcus	1.55	1.78	0.09	−2.52
Middle temporal gyrus	2.30	2.68	0.14	−2.67
Transverse temporal sulcus	1.52	2.27	0.26	−2.90
Inferior temporal sulcus	1.79	2.38	0.20	−2.93
Inferior parietal gyrus-supramarginal	2.09	2.49	0.14	−2.94
Precentral sulcus-inferior part	1.73	2.21	0.16	−2.96
Anterior collateral sulcus-transverse	1.89	2.63	0.25	−2.97
Inferior parietal gyrus-angular	2.20	2.55	0.12	−2.98
Inferior frontal gyrus-opercular	2.18	2.56	0.12	−3.02
Posterior lateral fissure	1.82	2.21	0.13	−3.10
Occipitotemporal med and lingual sulcus	1.93	2.42	0.16	−3.11

Table 3. (*continued*)

	C.M.	*Control Mean*	*Control SD*	*Z score*
TP	2.26	3.21	0.29	−3.32
Occipitotemporal med-parahip. gyrus	1.88	3.12	0.33	−3.79
Superior temporal gyrus-polar plane	2.26	3.36	0.27	−4.12
STS	1.76	2.33	0.13	−4.47
entorhinal_exvivo.label	1.68	3.37	0.36	−4.68
BA 44	1.83	2.40	0.12	−4.72
Superior temporal gyrus-temporal plane	1.68	2.40	0.15	−4.89
Superior lateral temporal gyrus	2.03	2.83	0.16	−5.18
Surface ROI in the right hemisphere				
Anterior cingular gyrus and sulcus	3.04	2.55	0.11	4.26
Suborbital sulcus	3.35	2.50	0.35	2.39
Inferior temporal gyrus	2.31	2.67	0.18	−2.03
Superior temporal gyrus-polar plane	2.66	3.28	0.29	−2.16
entorhinal_exvivo.label	2.14	3.38	0.40	−3.09

[a]C.M.'s mean cortical thickness in the right hemisphere was not significantly different from the control participants'.

On the right side, the loss of volume in the spheres projected onto the patient's brain reached the significance level for only 2 spheres out of 16 (z scores mean = −0.21, range = 0.96 to −4.69) and was relatively small in these two spheres (1.94% and 9.13%).

SOCIOEMOTIONAL BEHAVIOR ASSESSMENT

Given that the interpersonal behavioral changes observed in semantic dementia could be attributed to a ToM impairment (see, e.g., Duval et al., 2012), we assessed whether C.M.'s brain atrophies impacted on his socioemotional behavior.

Method

We used the Iowa Rating Scales of Personality Change (IRSPC; Barrash, Anderson, Jones, & Tranel, 1997; adapted in French by Juillerat & Peter-Favre, 1999, cited in Meulemans, Van Der Linden, Seron, & Juillerat, 2000) and the Interpersonal Reactivity Index (IRI; Davis, 1983; adapted in French by Guttman & Laporte, 2000). On the IRSPC, the patient's spouse was asked to rate 29 characteristics belonging to social and/or emotional or cognitive domains by choosing on a 7-point scale the level of dysfunction corresponding to the patient's behavior, both currently and before the onset of the brain injury. A difference of 3 points or more when comparing ratings pre- vs. post-onset of brain injury is considered as significant. The IRI includes 28 items, with half of the items assessing "affective aspects of empathy" ("personal distress" subscale, 7 items; "empathic concern" subscale, 7 items) and the other half of the items assessing "cognitive aspects of empathy" ("perspective taking" subscale, 7 items; "fantasy" subscale or the ability to imaginatively transpose oneself into fictional situations, 7 items). The IRI has been adapted so that the patient's spouse was asked to indicate on a 5-point scale how well each of the statements described her husband's behavior both currently and before the onset of the brain injury. Like other authors (see, e.g., Calabria, Cotelli, Adenzato, Zanetti, & Miniussi, 2009; Lough et al., 2006), we used the Wilcoxon signed-rank test to compare pre- versus postmorbid scores.

Results

On the IRSPC, a significant (and large, 4–6 points) difference pre- versus post-brain injury was found on the "depression" dimension and on some aspects related to the patient's executive functioning, such as whether the patient shows a "poor judgment" and is "easily overwhelmed" and, most importantly in the context of this study, several dimensions belonging to the interpersonal and/or emotional spheres. C.M. was perceived as having easily fits of anger, behaving sometimes aggressively, being inflexible, and quite insensitive to other people's emotions, whereas he was particularly calm, gentle, flexible, and sensitive to other people's emotions before his neurological pathology (qualities that made a lot of people appreciate C.M. as a pastor).

On the IRI, significant changes were found on the "personal distress" subscale (before = 4, current = 18; Wilcoxon signed rank test: $z = 1.84$, $p = .06$). However, closer inspection of the items for which significant changes were observed revealed that they did not necessarily

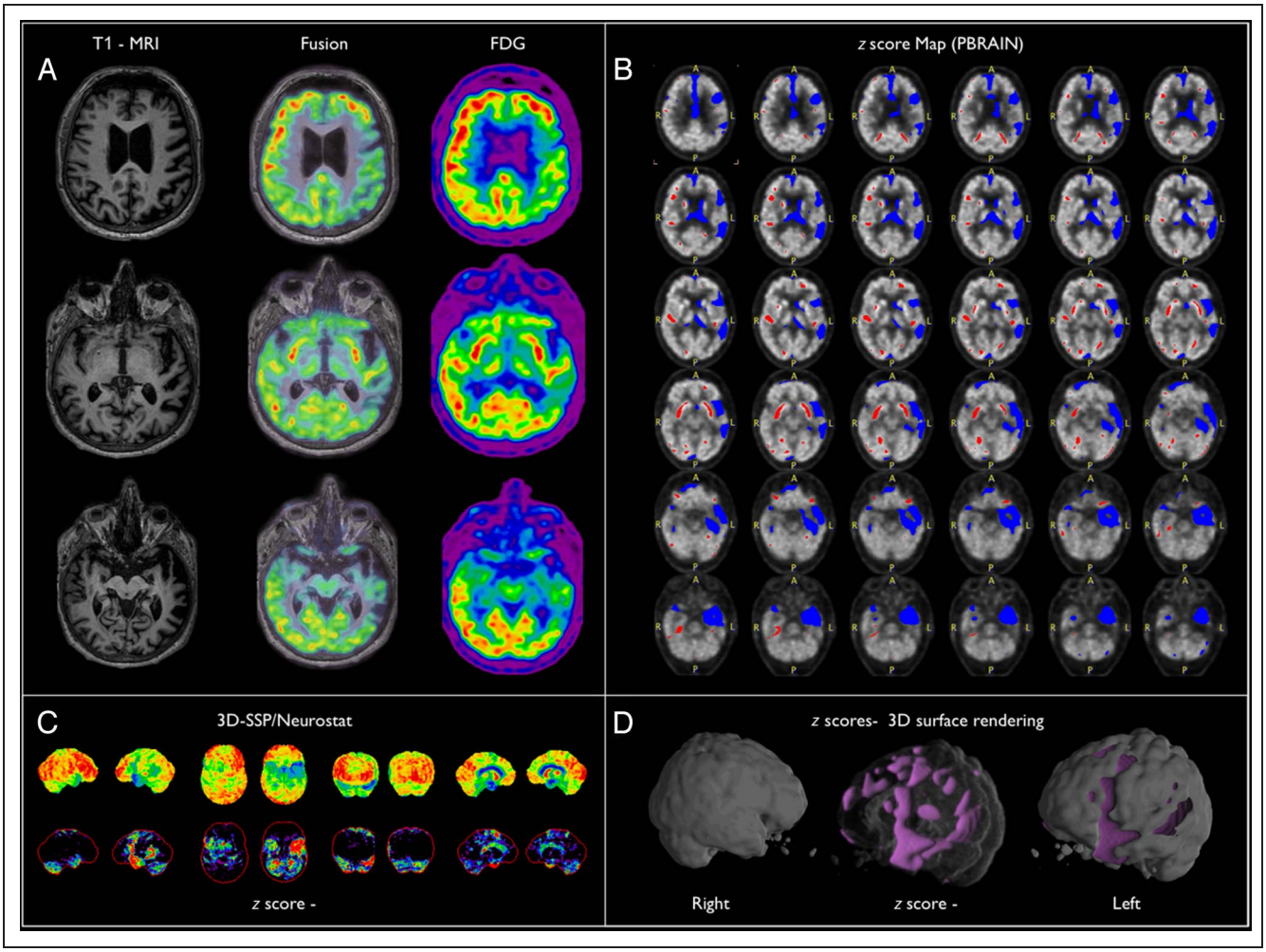

Figure 1. (A) Coregistration of the FDG PET acquisition in C.M. with the 3-D MRI. (B) Map distribution of the negative (blue) or positive (red) *z* scores comparing C.M. with healthy participants, surimposed to the FDG distribution. (C and D) 3-D volume rendering of the *z*-score deficits distribution generated with neurostat/ED-SSP software (C) and with PMOD module (D).

describe situations involving other people. The changes reported by the patient's spouse seemed to be related to the patient's increased difficulty to control his own emotions, particularly in emergency and/or emotional situations. Note that, according to some authors, the whole subscale might actually not really measure the patient's empathy but rather self-orientated emotional responses (see, e.g., Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004). Significant changes were also observed on the "perspective taking" subscale (before = 20, current = 4; Wilcoxon signed rank test: $z = -2, p < .05$). As perceived by his spouse, C.M. was much less prone to consider other people's perspective in everyday life situations than he was before his brain injury. No significant changes were observed on the "fantasy" (before = 6, current = 6) and on the "empathic concern" (before = 16, current = 8) subscales (Wilcoxon signed rank tests: $z = 0.00, p = 1$; $z = -1.46, p = .14$, respectively).

In summary, although the main difficulties spontaneously reported by the patient and his relatives did not concern the patient's relational or emotional behavior, these behaviors seemed to be also affected, to some extent, by his brain degeneration.

TOM ASSESSMENT

To examine directly how C.M.'s lesion to the left TP impacts on his ToM abilities, we presented him with five entirely nonverbal tasks requiring ascribing three types of mental states to other people, namely, intentions, knowledge, and beliefs.

The tasks were also administered to five healthy right-handed male participants matched to the patient for age (mean age = 61.2 years, range = 56–62 years) and education (secondary education and evening classes, without any higher qualification). All controls gave their written consent. Except when the *SD* was nil in the controls' scores, Crawford and Howell's (1998) modified *t* test was used to compare C.M.'s scores with the control group's scores. In each task, practice items were administered to ascertain that the patient and the control subjects understood the task instructions.

Table 4. Most Representative Deficits of Regional FDG Uptakes in C.M. Compared with 32 Healthy Participants

	z Scores Mean (SD)
AAL_vois Atlas	
Right hemisphere	
Frontal sup medial	−1.35 (1.26)
TP mid	−1.40 (0.88)
Cingulum mid	−1.47 (1.07)
Left hemisphere	
Cingulum mid	−1.50 (1.14)
Frontal inf (pars triangularis)	−1.52 (1.54)
Temporal sup	−1.60 (1.24)
Pallidum	−1.70 (0.51)
Precentral	−1.76 (1.58)
Caudate	−1.83 (1.24)
Supplementary motor area	−1.93 (1.46)
TP sup	−1.96 (1.93)
Temporal inf	−2.17 (1.34)
Thalamus	−2.19 (1.76)
Parahippocampal	−2.31 (1.13)
Temporal mid	−2.38 (1.58)
Frontal inf (pars opercularis-area 44)	−3.13 (1.51)
TP mid	−3.31 (1.48)
HA_n30r83	
Right hemisphere	
aTL-superior gyrus	−1.32 (0.82)
aTL-inferolateral	−1.49 (0.77)
Cingulate posterior	−1.52 (0.95)
Subcallosum area	−1.65 (0.42)
Cingulate anterior	−1.73 (1.01)
Left hemisphere	
Posterior temporal lobe	−1.39 (1.65)
Insula and cingulate anterior gyrus	−1.41 (0.98)
Insula and cingulate posterior gyrus	−1.41 (1.13)
Pallidum	−1.58 (0.61)
Nucleus accumbens	−1.78 (0.71)
Caudate nucleus	−1.90 (1.33)
Subcallosum area	−2.09 (0.53)
Hippocampus	−2.15 (1.01)
Frontal lobe-inferior frontal gyrus	−2.23 (1.60)
Thalamus	−2.24 (1.63)
Gyrus temp midin	−2.26 (1.28)
Gyrus parahippoc. and ambient	−2.84 (1.18)
aTL med	−2.95 (1.14)
aTL−superior gyrus	−3.45 (0.93)
Gyrus fusiform	−3.48 (0.92)
aTL: infero-lat	−3.93 (0.85)

Attributing Intentions to Others

Attributing intentions has been shown to activate both the right TP/aTL (e.g., Walter, Adenzato, & Ciaromidaro, 2004) and the left TP/aTL (e.g., Völlm et al., 2006; Walter et al., 2004; Brunet, Sarfati, Hardy-Baylé, & Decety, 2000). Moreover, attributing this type of mental states has been shown to be impaired in semantic dementia patients (at least at the group level, although there was a striking variability between patients' performance; Duval et al., 2012), putatively because of the patients' (left and/or right) TP(s)' atrophy. If the left TP is indeed necessary for intention attribution, we should expect that C.M.'s ability to reason about other people's intentions would be impaired.

Method

We used the nonverbal task designed by Sarfati and colleagues (Sarfati, Brunet, & Hardy-Baylé, 2003; Sarfati, Hardy-Baylé, Besche, & Widlöcher, 1997), which was used in previous neuroimaging (Völlm et al., 2006; Brunet et al., 2000) and neuropsychological studies (Duval et al., 2012). Each trial consisted of a sequence of three pictures. At the end of each sequence, participants were asked to choose among three choice pictures the one that shows the logical ending of the story. In the critical ToM condition ($n = 28$), predicting the ending of the story required inferring the intention of the human protagonist. In the non-ToM conditions (involving characters, $n = 14$, or only objects, $n = 14$), predicting the ending of the story required reasoning about physical causality.

Results

C.M. scored 23/28 on the critical ToM condition, a performance falling within the range of the controls' scores (22–28, mean = 25.6/28; modified t test: $t(4) = -1.03$; $p_{\text{one-tailed}} = .18$). In the two control conditions, C.M. correctly chose the logical ending of the story in all trials (see Figure 3). Thus, in comparison with controls, C.M.

Table 5. Loss of Volume in C.M.'s Brain Compared with 13 Healthy Controls' Brains, in the Spheres Corresponding to 31 Foci of ToM Activation Observed in the TPs or More Widely in the aTLs in Neuroimaging Studies

x	*y*	*z*	*Corresponding Brain Region*[a]	*Study*	*Mental States Category*[b]	*Verbal or Nonverbal ToM Task*[c]	*Controls' Mean Voxels Number Preserved/515*[d]	*C.M.'s Voxels Number Preserved*	*z Score*
Right									
50	10	−28	Anterior STS	Saxe and Powell (2006)[e]	Beliefs	Verbal	347.92 (67.56%; 19.42)	444 (86.21%)	0.96
35	14	−31	TP (BA 38)	Gobbini et al. (2007)	Beliefs	Verbal	418.77 (81.31%; 21.81)	505 (98.06%)	0.77
57	3	−21	BA 21/38	Völlm et al. (2006)	Emotions	Nonverbal	368.38 (71.53%; 18.18)	429 (83.3%)	0.65
54	0	−21	BA 21	Walter et al. (2004)	Intentions	Nonverbal	488.15 (94.79%; 9.23)	515 (100%)	0.56
53	−18	−17	Anterior STS	Saxe et al. (2006)[e]	Beliefs	Verbal	506.08 (98.27%; 3.62)	515 (100%)	0.48
42	6	−28	TP adjacent to amygdala (BA 38)	Castelli, Frith, Happé, and Frith (2002)	Intentions	Nonverbal	512 (99.42%; 0.9)	514 (99.81%)	0.43
46	14	−13	TP (BA 38)	Schultz et al. (2003)	Intentions	Nonverbal	449.54 (87.29%; 17.5)	483 (93.79%)	0.37
39	16	−29	TP	Spiers and Maguire (2006)[e]	Other	Nonverbal	413.77 (80.34%; 19.13)	449 (87.18%)	0.36
34	6	−26	TP adjacent to amygdala (BA 38)	Castelli, Happé, Frith, and Frith (2000)	Intentions	Nonverbal	511.38 (99.3%; 2.25)	515 (100%)	0.31
32	8	−31	STG (BA 38)	Nieminen-von Wendt et al. (2003)	Other	Verbal	469.46 (91.16%; 13.96)	483 (93.79%)	0.19
58	4	−14	MTG (BA 21/38)	Castelli et al. (2010)	Other	Verbal	331.85 (64.44%; 19.63)	347 (67.38%)	0.15
46	−2	−16	Anterior STS (BA 21)	Ferstl and von Cramon (2002)	Other	Verbal	512 (99.42%; 1.23)	509 (98.83%)	−0.47
48	4	−33	MTG/TP	Völlm et al. (2006)	Emotions	Nonverbal	322.23 (62.57%; 24.05)	254 (49.32%)	−0.55
56	−10	−13	Middle STS (BA 21)	Rilling et al. (2004)	Intentions	Nonverbal	501.15 (97.31%; 3.47)	485 (94.17%)	−0.90
49	5	−17	BA 21	Gobbini et al. (2007)	Intentions	Nonverbal	505.54 (98.16%; 3.58)	468 (90.87%)	−2.03*
53	−18	−12	Anterior STS	Saxe and Kanwisher (2003)[e]	Beliefs	Verbal	514.08 (99.82%; 0.38)	505 (98.06%)	−4.69*

Left

−62	−32	14	Superior MTG	Castelli et al. (2010)	Other	Verbal	387.54 (75.25%; 18.14)	255 (49.51%)	−1.42
−63	−15	−15	BA 21	Walter et al. (2004)	Intentions	Nonverbal	369 (71.65%; 13.34)	240 (46.6%)	−1.88
−50	12	−26	TP (BA 38)	Gobbini et al. (2007)	Beliefs	Verbal	329.54 (63.99%; 24.71)	7 (1.36%)	−2.53*
−45	10	−31	BA 21/38	Völlm et al. (2006)	Emotions	Nonverbal	356.08 (69.14%; 25.05)	13 (2.52%)	−2.66*
−38	−4	−32	TP adjacent to amygdala (BA 38)	Castelli et al. (2000)	Intentions	Nonverbal	493.62 (95.85%; 7.74)	386 (74.95%)	−2.70*
−57	−3	−18	Anterior MTG (BA 21)	Farrow et al. (2001)	Other	Verbal	467.85 (90.84%; 12.66)	288 (55.92%)	−2.76*
−59	−21	−7	MTG, extending to TP	Völlm et al. (2006)	Intentions	Nonverbal	488.62 (94.88%; 6)	346 (67.18%)	−4.62*
−44	14	−16	STG (BA 38)	Goel et al. (1995)	Knowledge	Nonverbal	493.92 (95.91%; 8.92)	239 (46.41%)	−5.55*
−55	−47	4	MTG (BA 21)	Russell et al. (2000)	Other	Verbal	503.23 (97.71%; 2.92)	410 (79.61%)	−6.19*
−55	−31	9	STG (BA 22)	Russell et al. (2000)	Other	Verbal	484.08 (94%; 8.29)	190 (36.89%)	−6.89*
−48	11	−18	TP (BA 38)	Gobbini et al. (2007)	Intentions	Nonverbal	484 (93.98%; 6.6)	205 (39.81%)	−8.21*
−44	0	−28	TP (BA 21)[f]	Calarge et al. (2003)	Other	Verbal	510.92 (99.21%; 1.8)	434 (84.27%)	−8.28*
−38	8	−16	STG (BA 38)	Brunet et al. (2000)	Intentions	Nonverbal	481.46 (93.49%; 6.77)	38 (7.38%)	−12.71*
−28	10	−26	TP (BA 38)	Mano, Harada, Sugiura, Saito, and Sadato (2009)[e]	Emotions	Verbal	511.38 (99.3%; 1.71)	357 (69.32%)	−17.49*
−54	−13	−8	Anterior STS (BA 21)	Ferstl and von Cramon (2002)	Other	Verbal	509.62 (98.95%; 1.37)	310 (60.19%)	−28.25*

[a]Corresponding brain region: STS = superior temporal gyrus; TP = temporal pole; BA = Brodmann's area; STG = superior temporal gyrus; MTG = middle temporal gyrus.

[b]Mental states category: the peak activations reported in studies requiring from participants to reason about mental states, which did not clearly or uniquely belong to the "belief," "emotions," "intentions," or "knowledge" categories have been coded as "other." For example, in Spiers and Maguire's (2006) study, participants were prompted to reason spontaneously about the thoughts and intentions of other people. In Nieminen-von Wendt et al.'s (2003) study, participants were presented with "strange stories" developed by Happe (1994), which require reasoning about various mental states such as thoughts, feelings, and desires. Castelli et al. (2010) and Russell et al. (2000) used (adaptations of) the "Reading the mind in the eyes" test, developed by Baron-Cohen et al. (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997), which requires participants understanding what a person is feeling or thinking.

[c]Only entirely nonverbal ToM tasks have been classified as "nonverbal." The "Ultimatum game" and the "Prisoner's Dilemma Game" used in Rilling, Sanfey, Aronson, Nystrom, and Cohen's (2004) study have been classified as nonverbal ToM tasks.

[d]Controls' mean voxels number preserved: mean number of voxels preserved out of 515 in the spheres projected onto the controls' brains (value in percentage and standard deviation of the percentage value).

[e]Studies for which the reported MNI coordinates have been transfered into the Talairach coordinates.

[f]Although the corresponding Brodmann's area reported in Calarge, Andreasen, and O'Leary's (2003) study is BA 21, the reported peak of activation is in the TP.

*Significant z scores.

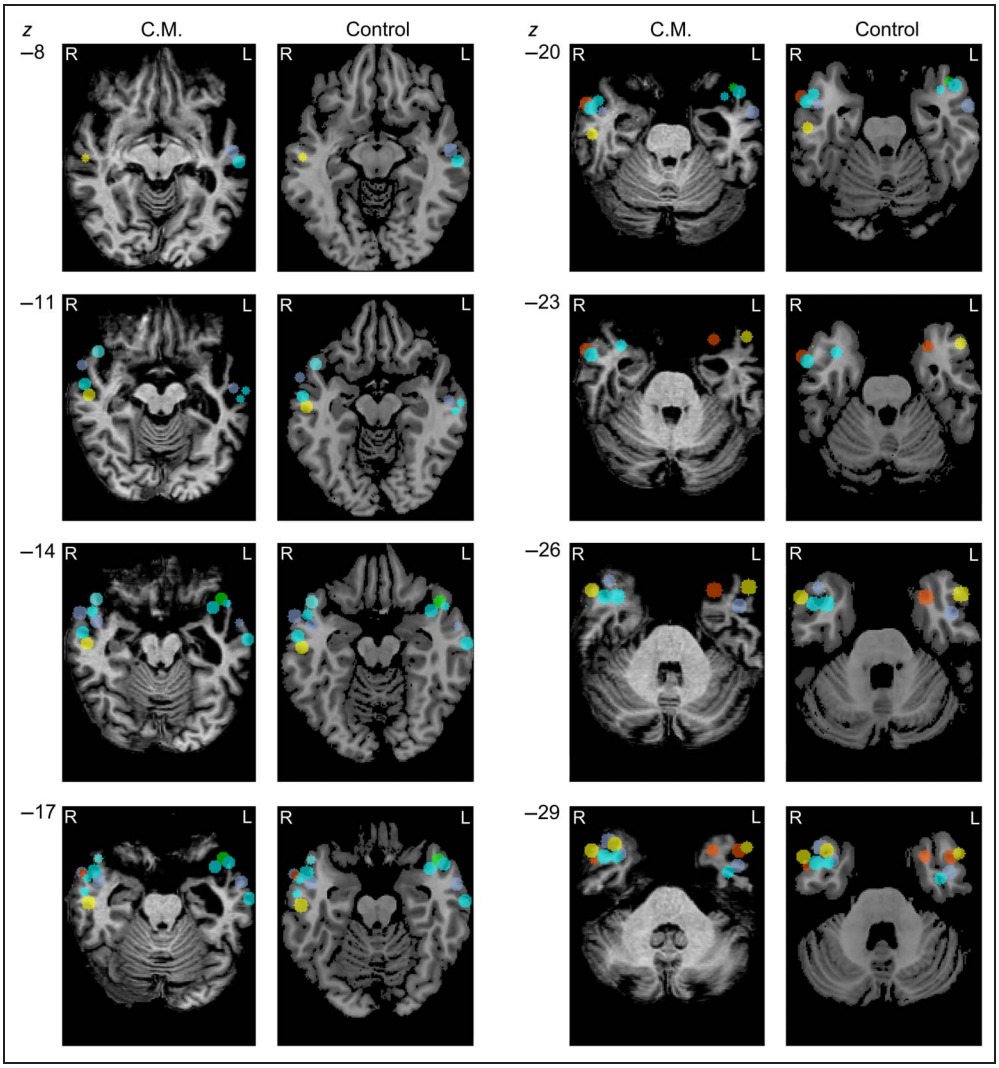

Figure 2. Foci of ToM activation in the TPs/aTLs reported in neuroimaging studies listed in Table 5, projected onto C.M.'s and one healthy participant's anatomical data transformed into Talairach space, as spherical volumes of 515 mm^3 around the Talairach coordinates reported in the studies. The color dots correspond to peaks of activation reported in studies involving belief attribution (yellow), emotion attribution (red), knowledge (green), intention (blue), or other types of mental states (gray; see Table 5 for details about this category). Note: for purposes of illustration, we projected the foci onto only one healthy participant's anatomical data rather than onto the average and represented only brain sections corresponding to one of three *z* values between −8 and −29.

did not show an impaired ability to infer other people's intentions.

Attributing Knowledge States to Others

Attributing knowledge states and their negative counterpart, ignorance states, have also been shown to activate the left TP (see Goel, Grafman, Sadato, & Hallett, 1995). Ascribing a knowledge state to somebody else requires understanding the relation between what is known (e.g., a specific object property such as its color or texture) and how knowledge was gained (e.g., through seeing or touching; e.g., O'Neill, Astington, & Flavell, 1992). If the left TP is necessary to understand the relation between a source of knowledge and the resulting knowledge state, we should expect that this understanding would be impaired in C.M.

Method

Two entirely nonverbal tasks were used to assess C.M.'s ability to infer knowledge other people gain from various physical interactions with objects. The first task assessed reasoning about four different knowledge sources (seeing, touching/weighting, tasting, and smelling). It consisted of 24 short nonverbal videos showing three actors each making a different action toward two containers. Participants were presented with a pair of target objects and were asked to choose which actor knew in which of the two containers each target object was located. Crucially, the target objects varied across trials, and each pair of objects differed according to some, but not all, sensory properties (e.g., two different drinks like Coke and Fanta—same quantity—have the same weight but do not taste the same; a big vs. a small quantity of water have an identical taste but a different weight; water vs. white rum have the same visual aspect but do not smell the same; a yellow vs. a pink Post-it have the same weight but a different visual aspect, etc.). On each trial, one actor made a relevant action to locate the target objects (e.g., lifting the two containers to find out which of them contained a stapler and which of them contained a driving license), another actor made a sensorial action that gave access to an irrelevant property of the objects (e.g., smelling the content of the two containers to find

out which one contained the stapler and which one contained the driving license), and a third actor made an action which gave no information about the object properties (e.g., blowing on the containers). The order of presentation of the three actions was counterbalanced across trials. The design of the task allowed detecting not only full loss of understanding but also incomplete understanding of how knowledge is acquired. Indeed, if a patient still understands that sensory experiences are necessary to gain sensory information about objects but does not understand anymore which specific knowledge about the objects can be gained from specific sensorial actions toward them, he should avoid choosing the actor who made a nonsensorial action but may sometimes erroneously choose the actor who made an irrelevant sensorial action (for a similar proposal in the developmental literature, see e.g., O'Neill et al., 1992).

The second task (Samson et al., unpublished) examined the reasoning about two sources of knowledge (weighting and seeing). In this task, the participant was presented with 36 short nonverbal videos. The task consisted in locating an object in one of two containers: either a Post-it (on top of one of the containers) or a weight (inside one of the containers). The two containers were hidden under a blanket. Two actors made an action toward the containers (either looking under the blanket without touching the containers or lifting the containers without removing the blanket), only one of them being relevant for the target object to be found (looking being relevant to find the Post-it and lifting being relevant to find the weight). After their actions, the actors pointed to one of the two containers. On the critical ToM trials (n = 24), each actor pointed to a different box. Finding the object location thus required inferring who had gained relevant knowledge based on the action performed. The task included also filler trials (n = 12), in which the two actors pointed to the same box.

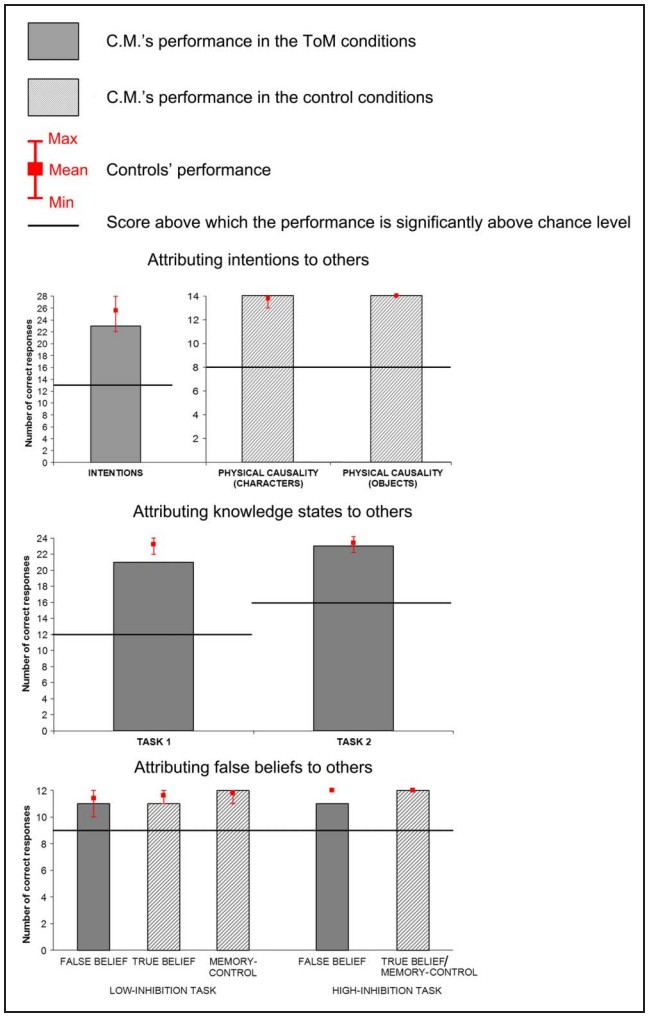

Figure 3. C.M.'s performance in the five nonverbal ToM tasks.

Results

C.M. scored 21/24 on the first task, a performance just below the range of performance of the controls (22–24, mean = 23.2/24; modified t test: $t(4) = -2.39$, $p_{\text{one-tailed}} = .04$). However, it is worthwhile noting that the three errors C.M. made in this task did not reveal any failure to understand the relationship between the action performed and the type of knowledge gained by the actor. Indeed, two of three errors were because of the fact that C.M. had not seen that one actor wore a headband over the nose and not over the eyes. This led C.M. to incorrectly infer that this actor had smelt the content of the boxes and was consequently well informed in one trial and led C.M. to incorrectly infer that this actor could not see the content of the containers in the other trial. The third error C.M. made consisted in choosing the nonsensorial action of rubbing the external side of the box with the back of the hand to find in which boxes a felt-tip pen and a driving license were located, respectively. C.M. spontaneously justified his choice by explaining with gestures that this action might have made the objects move within the boxes and thus might have given the actor an idea about which kind of object (lighter object with silent movement or heavier object with noisy movement) was within each metallic container.

In the second task, C.M. performed within the range of performance of the controls, making only one error (controls' mean score = 23.4/24, range = 22–24, $t(4) = -0.41$, $p_{\text{one-tailed}} = .35$). Thus, in both tasks and in comparison with controls, C.M. did not show an impaired understanding of how knowledge states are acquired by sensory experiences.

Attributing False Beliefs to Others

False-belief reasoning is at the core of the most widely used tasks designed to assess ToM skills and has been shown to involve the right and/or left TP(s) or wider aTL(s) in neuroimaging studies (e.g., Gobbini, Koralek,

Bryan, Montgomery, & Haxby, 2007; Saxe & Powell, 2006; Saxe, Schulz, & Jiang, 2006; Saxe & Kanwisher, 2003). Importantly, false-belief reasoning (as assessed in verbal tasks) has also been shown to be impaired in semantic dementia patients putatively because of the patients' atrophy of the (left and/or right) TP(s) (Duval et al., 2012). If the left TP is necessary for false-belief reasoning, we should expect C.M.'s ability to infer false beliefs to be impaired.

Method

We used two nonverbal false-belief reasoning tasks developed by Apperly and Samson (Samson, Apperly, Kathirgamanathan, & Humphreys, 2005; Apperly, Samson, Chiavarino, & Humphreys, 2004; Samson et al., 2004). In the "low-inhibition false-belief task," the participants were presented with short nonverbal videos and were asked to locate an object in one of two containers on the basis of where another person is pointing at. On the critical false-belief trials (n = 12), correctly locating the object required understanding that the other person pointed to the wrong container because she had a false belief about the object's location. At the point in time where the participant could infer that the other person had a false belief, the participant himself did not know where the object was really located (there was thus no need to resist interference from one's own knowledge of the true location of the object). False-belief trials were mixed with true-belief trials (n = 12) in which the person pointed to the right container based on a true belief about the object's location and with memory control trials (n = 12) and filler trials (n = 12), which did not require reasoning about the person mental state (for details about the method, see Apperly et al., 2004; Samson et al., 2004).

The "high-inhibition false-belief task" also consisted of short nonverbal videos, but this time, the task was to predict which of two containers another person would open first to find an object. On the critical false-belief trials, the correct answer required inferring that the other person had a false belief and would therefore open the box where the object was not located. In this task, at the time the participant could infer that the other person had a false belief, the participant himself knew where the object was really located and had thus to inhibit his own knowledge of the true location of the object. False-belief trials (n = 12) were mixed with true-belief trials that also acted as memory control (n = 12) and with filler trials (n = 12; for details about the method, see Samson et al., 2005). C.M. and the control subjects were presented with the low-inhibition false-belief task first, followed by the high-inhibition false-belief task.

Results

C.M. made only one error on the critical false-belief trials in each task, a performance equivalent to the controls' (low-inhibition false-belief task: controls' range = 10–12, mean = 11.4/12; modified t test $t(4) = -0.46$, $p_{\text{one-tailed}} = .34$; high-inhibition false-belief task: controls' mean score = 12/12, modified t test nonapplicable because of the *SD* being nil in the controls' scores). This performance on the critical false-belief trials was observed in the context of a good performance on the other categories of trials, with only one error on the "true-belief" trials of the low-inhibition false-belief task (controls' range = 11–12, mean = 11.6/12; modified t test: $t(4) = -1.12$, $p_{\text{one-tailed}} = .16$) and two errors on the filler trials in the high-inhibition false-belief task (controls' mean score = 12/12, modified t test nonapplicable because of the *SD* being nil in the controls' scores). Thus, C.M.'s correct inference of false beliefs did not result from the use of a superficial strategy (e.g., always responding to the box opposite to the one the woman pointed at in the low-inhibition false-belief task). It can thus be concluded that, in comparison with controls, C.M. did not show an impaired ability to attribute false beliefs to other people.

Summary of C.M.'s Performance on Nonverbal ToM Tasks

For purposes of illustration, C.M.'s overall performance on nonverbal ToM tasks is shown in Figure 3. It clearly appears that C.M.'s ability to reason about other people's mental states in nonverbal contexts, whether these are intentions, knowledge, or false beliefs, was unaffected by his damage to the left TP.

DISCUSSION

We reported the case of a patient diagnosed with semantic dementia whose brain atrophy and hypometabolism severely affected the left TP. Most portions of the left TP (and of the wider left aTL) that have been shown to be preferentially activated in neuroimaging studies when healthy adults reason about other people's mental states were massively affected, whereas the corresponding areas on the right side were relatively spared. This patient had thus the potential to provide valuable insights into the question of whether the left TP is necessary for successful ToM reasoning or not. Given the patient's language deficits, his ToM abilities were assessed using a battery of entirely nonverbal tasks. Interestingly, across five different ToM tasks encompassing 100 trials that probed the patient's ability to attribute different mental states (intentions, knowledge, and beliefs), no impairment was observed in the patient's performance. This pattern suggests that the left TP is not necessary for ToM reasoning, at least in conditions that require no linguistic processing and as far as "cognitive ToM" is concerned (the patient's ability to ascribe affective mental states or "affective ToM" could not be tested because of a lack of availability of nonverbal tasks). In principle, three issues could undermine this conclusion. First, it could be argued that C.M.'s left TP was

not sufficiently damaged to interfere with his ToM abilities. Although this possibility cannot be completely excluded, it is worth reminding that among the 15 subregions of the left TP/aTL that were associated with ToM in previous studies, 13 were significantly atrophied in C.M.'s brain (including subregions that are usually activated in nonverbal ToM tasks), with the loss of white and/or gray matter being larger than 50% in six of these regions. Thus, it seems very unlikely that any still functional parts of the left TP were sufficient on their own to perform the tasks at the high level of performance shown by C.M.

Second, it could be argued that C.M. solved the nonverbal ToM tasks without genuine ToM reasoning. Indeed, several authors have proposed that some nonverbal ToM tasks can be solved by low-level processes without requiring reasoning about mental states at a higher conceptual level. Such explanation has been put forward to explain how infants (e.g., Kovács, Téglás, & Endress, 2010; Onishi & Baillargeon, 2005) and nonhuman species (e.g., Hare, Call, & Tomasello, 2006; Melis, Call, & Tomasello, 2006; for a review, see Call & Tomasello, 2008) solve some nonverbal ToM tasks (for a discussion, see Apperly & Butterfill, 2009). According to this account, the left TP might still be necessary for ToM reasoning, but this would only appear when confronting brain-damaged patients with verbal ToM tasks, such as those used by Duval et al. (2012) or Rankin et al. (2009), in which low-level associations bypassing the conceptual level cannot help. However, it is very hard to conceive that low-level associations alone were sufficient to pass all the nonverbal ToM tasks we used in this study. For example, the two knowledge inference tasks required associating various actions to various invisible object features (such as taste, smell, or weight), and it is hard to envisage how such diverse links could have been made by superficial associations.

Third, one could argue that our nonverbal ToM tasks were not sensitive enough to detect a ToM impairment. It is important to stress here that the exact same nonverbal intention attribution task has been used before to show ToM impairments in various populations including patients with semantic dementia (Duval et al., 2012) and patients with schizophrenia (Brunet, Sarfati, Hardy-Baylé, & Decety, 2003). As mentioned before, this is also a task that showed left TP activation in fMRI studies (Völlm et al., 2006; Brunet et al., 2000). The exact same nonverbal false-belief tasks have also been used before, this time to show ToM impairments following nondegenerative brain pathologies (Samson et al., 2004, 2005; Apperly et al., 2004). Furthermore, there is direct evidence that the low-inhibition false-belief task that we used is as sensitive as its verbal counterpart to detect impairments (Apperly et al., 2004), and there is evidence that the high-inhibition false-belief task that we used is sensitive enough to detect effects of normal aging on ToM (Bailey & Henry, 2008). It could still be objected that first-order belief reasoning tasks like the ones we used are too easy compared with second-order belief reasoning tasks (e.g., Mary wrongly thinks that John wrongly thinks that the ball is in the garage). Note, however, that even first-order false-belief reasoning was shown to be impaired in semantic dementia patients (with bilateral damage to the TPs) examined previously (see Duval et al., 2012).

In summary, if the left TP was necessary for ToM reasoning, C.M. should have shown some level of impairment in the ToM tasks used in this study.

Previous studies that found a ToM impairment (Duval et al., 2012; Rankin et al., 2009; Stone et al., 2003) or changes in the patients' social behavior, which may be related to a ToM impairment (Rankin et al., 2006; Snowden et al., 2001; Bozeat et al., 2000; Edwards-Lee et al., 1997; Ghika-Schmid et al., 1995; Lilly et al., 1983; Terzian & Ore, 1955) following damage to the TP(s), were compatible with all possibilities as to whether the left and/or right TPs are necessary for successful ToM reasoning or not. We can now narrow down to three possibilities.

The first remaining possibility is that only the right TP is necessary for ToM reasoning. In this case, the processes sustained by the left TP could be prompted by, but not necessary for, the reasoning about other people's mental states. For example, the left TP activation might reflect the access to autobiographical memories, social scripts, and/or social concepts (Ross & Olson, 2010; Frith & Frith, 2003; Gallagher & Frith, 2003), but this information would not be crucial for solving ToM tasks. It is also possible that the left TP activation reflects the deployment of other processes, which are not necessary to solve (nonverbal) ToM tasks, such as word production processes (see, e.g., Bi et al., 2011; Schwartz et al., 2009). For example, healthy participants may spontaneously verbalize when faced with ToM scenarios even if it is not necessary to do so to solve the task.

In this first remaining scenario, a significant impairment of ToM abilities would only be found after damage to the right TP, as it was the case in patient S.E. reported by Stone et al. (2003) and in semantic dementia patients with bilateral TP damage involved in studies by Duval et al. (2012) and Rankin et al. (2009). Future studies would speak in favor of this first remaining possibility if they can demonstrate that unilateral damage to the right TP impacts on a patient's ToM abilities.

The second remaining possibility is that only one TP is necessary for ToM, so that successful ToM reasoning can be achieved as long as either the left or the right TP is spared. This could be the case if the left and the right TPs redundantly contribute to ToM reasoning, for example, by sustaining the processing of information (autobiographical memories, social scripts, or social concepts) necessary to solve ToM tasks, in a way that parallels the redundant contribution of the left and right aTLs to the representation of object conceptual knowledge (see Lambon Ralph et al., 2001, 2010, 2012). In this second case, each TP would be sufficient for ToM reasoning so that a unilateral damage to one of them would not impact on ToM abilities. A significant impairment of ToM abilities

would only be found after a bilateral damage to the TPs, as it seemed to be the case in semantic dementia patients involved in studies by Duval et al. (2012) and Rankin et al. (2009). This second remaining possibility would be confirmed in future studies if ToM abilities were still preserved following unilateral damage to the right TP but impaired following bilateral damage to the TPs.

The third and last remaining possibility is that neither the left nor the right TP are necessary for ToM. This would be supported by evidence showing that ToM abilities would be preserved even after a bilateral damage to the TPs. It would then follow that the ToM impairment observed previously in patients with semantic dementia (see Duval et al., 2012; Rankin et al., 2009) or other etiologies involving the TP(s) (Stone et al., 2003) was imputable to brain damage extending beyond the TPs. Alternatively, semantic dementia patients' ToM abilities may have been underestimated because of the use of verbal material. Indeed, as it is often the case in patients with semantic dementia (see Patterson et al., 2006) and exemplified in C.M.'s profile, these patients might have linguistic deficits that would have interfered with the understanding of verbal ToM vignettes or with the ability to verbally report the outcome of the ToM reasoning. In the latter case, the damage to the TPs (especially the left TP) might have been responsible for the impairment that semantic dementia patients show on ToM tasks, however, not because the TP(s) is/are necessary for ToM reasoning per se, but rather because of the need to use language in classic ToM tasks.

Further narrowing down of the possible possibilities regarding the involvement of the right and left TPs in ToM will require careful examination of the ToM performance of patients with well-delineated damage to the right TP and, if necessary, to the right and left TPs.

Although the current data clearly shows that the left TP is not necessary for ToM reasoning, the conclusion that the functional role sustained by the left TP is not necessary for ToM reasoning needs more cautious consideration. In cases like the one reported here, it cannot be excluded that a preserved brain region has fulfilled a compensatory role to support the cognitive processes that can no longer be sustained by the left TP (for empirical evidence of compensatory mechanisms in neurodegenerative disorders, see, e.g., van Nuenen et al., 2012; Stern et al., 2000). Should future studies show that such compensation is possible and that it is at the origin of the patients' success, our conclusion that the left TP is not necessary for ToM reasoning would be limited to the left TP as neural substrate. On the other hand, should future studies show that such compensation is not possible or that it is not at the origin of the patients' success, our conclusions could be more confidently extended to the left TP's functional role.

Our findings also inform on the issue of ToM abilities and, more generally, social abilities in semantic dementia. Two points deserve attention. First, the preservation of ToM abilities (in nonverbal contexts) in a patient with semantic dementia like C.M. does not mean that ToM abilities are necessarily preserved in all patients with semantic dementia. As suggested by previous studies (see Duval et al., 2012; Rankin et al., 2009) and discussed above, ToM abilities might be impaired if/when the atrophy significantly extends to the right TP. This possibility has to be investigated in further studies. It cannot be excluded either that a semantic dementia patient's ToM abilities would be affected if/when the atrophy more largely extends to regions in the frontal lobe that might be critical for ToM reasoning.

Second, a patient with semantic dementia like C.M., who is able to solve nonverbal ToM tasks such as those used in this study, is not necessarily immune from social difficulties in daily life. C.M. did present some difficulties in the social and emotional domains. This is an important point with respect to the consideration of patients' interpersonal difficulties: The preservation of the patient's ToM reasoning in (nonverbal) ToM tasks does not guarantee an appropriate social behavior (and conversely, abnormal social behavior in a patient with semantic dementia should not necessarily be considered as the behavioral signature of a ToM impairment). Indeed, a lot of information about people's mental states might be conveyed through language in daily life so that even a restricted inability to reason about other people's mental states on the basis of verbal cues might considerably impact on the patient's interpersonal relationships. Furthermore, the ability to infer other people's mental states is obviously not sufficient to efficiently navigate in our social environment. We also have to react appropriately to the inferred mental states and to be willing to take them into account, for example, in case of disagreement. These social competencies (emotional regulation, moral reasoning. etc.), which extend beyond the boundaries of classic ToM competencies and which are captured in scales measuring the patient's socioemotional behavior such as the IRI (used in this study), might also be vulnerable to brain degeneration. For example, the psychological impact of the illness, such as a higher degree of depression (also reported for C.M. in the IRSPC), might affect the way the patient behaves and more particularly the way the patient tends to react to other people's mental states/point of views. The patient's language deficits (outside the social domain) might also be responsible for communication difficulties, which might in turn encourage the patient to let himself be guided by his/her own ideas/point of view or might even lead the patient's acquaintances to perceive him/her as less prone to consider others' point of view.

In summary, the ability to reason about other people's mental states might be preserved in semantic dementia, at least in nonverbal contexts and as assessed with classic cognitive ToM tasks. However, this does not preclude from observing changes in the patient's social behavior, which might not be because of a ToM impairment. An open question remains whether ToM abilities are still

preserved when the brain atrophy extends to the right TP and/or to other brain regions.

Conclusions

In conclusion, we reported the case of a patient (C.M.) who suffered from a massive atrophy to the left TP while the right TP was relatively spared. The atrophy encompassed most portions of the left TP (and of the wider left aTL) that have been shown to be preferentially activated in neuroimaging studies when healthy adults reason about other people's mental states. Despite this atrophy, the patient did not show any impairment in his ability to attribute mental states (intentions, knowledge, beliefs) to other people. We therefore conclude that the left TP is not a necessary brain region for ToM reasoning, at least as long as the right TP is preserved. Further understanding of the TPs' involvement in ToM will require careful examination of the ToM performance of patients with well delineated damage to the right TP and, if needed, to the right and left TPs, to see whether successful ToM reasoning requires the involvement of the right TP, the involvement of one of the two TPs at least, or of neither.

Acknowledgments

We are very grateful to C.M. and his spouse for their generous collaboration. We also thank the control participants for their patience and willingness to participate in this study. Finally, we thank Marie-Pierre de Partz from the Cliniques Universitaires Saint-Luc for giving access to neuropsychological and language data of C.M. and for her help in the examination of these data and Gilles Vannuscorps (Université catholique de Louvain) for his help in testing C.M.'s language abilities and for his valuable comments on an earlier version of the manuscript. This research was supported by the FNRS Grant 1.B182.10 awarded to Caroline Michel (with Agnesa Pillon and Dana Samson as promoters).

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