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Reviews and perspectives

Theory of mind ability in the behavioural variant of frontotemporal dementia: An analysis of the neural, cognitive, and social levels

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ABSTRACT

The paper reviews convergent evidence on the ability to attribute mental states to one's self and to others (i.e., theory of mind, ToM) in patients affected by the behavioural variant of frontotemporal dementia (bv-FTD). This disease represents a particular challenge for researchers and clinicians, due to its insidious onset and ambiguous clinical features, which frequently render difficult a precise and timely diagnosis. The paper proposes a way to shed new light on the hypothesis that the neuropsychiatric profile of individuals with bv-FTD can be at least partially explained by a deficit in ToM ability. We examined both neuroimaging data on the neural correlates of ToM ability in healthy participants and studies investigating the progressive cerebral atrophy in patients with bv-FTD. Our findings suggest a link between the progressive degeneration of the anterior regions of medial frontal structures characterising the early stages of the bv-FTD and the ToM deficit these patients show. They also suggest the importance of using ToM tests during the diagnostic process of bv-FTD.

Contents

1. Introduction

The present work reviews convergent evidence on the ability to attribute mental states to one's self and to others (i.e., theory of mind, ToM) in patients affected by the behavioural variant of frontotemporal dementia (bv-FTD). In the early stages of this neurodegenerative disease, patients typically manifest behavioural and psychiatric problems. According to a recent proposal, the social and behavioural problems of these patients can be considered as being linked to a deficit in the domain of social cognition (Gregory et al., 2002; Kipps & Hodges, 2006; Lough & Hodges, 2002; Lough, Gregory, & Hodges, 2001; Lough et al., 2006; Snowden et al., 2003). Based on this suggestion, herein we hypothesise that the neuropsychiatric profile of bv-FTD patients is associated, at least partially, with a specific deficit in the ToM ability.

The following sections illustrate the usefulness of a social cognitive neuroscience approach that takes into due account the neural, cognitive, and social levels of analysis in the study of bv-FTD. Indeed, in the early stages of bv-FTD, it is possible to observe various signs and symptoms that pertain to these different domains (e.g., neural atrophy in the frontal lobes, personality changes and breakdown in social conduct), and their combination must be carefully weighed by clinicians when making a diagnosis. We support the view that the examination of these equally important levels can provide a more in-depth perspective on bv-FTD. In keeping with this, we examined neuroimaging data on the neural correlates of

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ToM ability, the studies investigating the progressive cerebral atrophy in patients with bv-FTD, and all of the studies investigating the ToM domain in these patients.

2. Anterior medial frontal cortex and theory of mind

In the last decade, there has been growing interest in the neural correlates of social cognition, defined as the ability to construct mental representations of the relations that exist between one's self and others and to flexibly use these representations to function effectively in the social environment (Adolphs, 2001, 2003). Social cognition is a sum of different processes and depends on the exchange of specific signals such as facial expression, body movement, and eye gaze (Frith & Frith, 2007). Examples of abilities referable to the domain of social cognition are both our capacity to represent other people's intentions and beliefs (ToM), and the capacity to share the emotions and sensations of others (empathy) (Lieberman, 2007). These distinct capacities display different ontogenetic trajectories reflecting the different developmental pathways of their underlying neural structures (Singer, 2006). In the present work we focus our attention on the former ability mentioned, i.e., ToM.

ToM (or mentalising) is defined as the ability to explain and predict other people's behaviour by attributing independent mental states to them (Baron-Cohen, 1995; Frith & Frith, 1999; Leslie, 1987; Premack & Woodruff, 1978). It allows us to recognise that mental states such as beliefs, intentions, and desires play a key role in driving human behaviour. Impairment in ToM ability can be highly disabling, as observed in various clinical syndromes, such as autism and certain manifestations of schizophrenia, which are characterised by ToM deficits (Baron-Cohen, Leslie, & Frith, 1985; Brüne, 2005; Brunet-Gouet & Decety, 2006; Corcoran, Mercer, & Frith, 1995; Hardy-Bayle, Sarfati, & Passerieux, 2003; Walter et al., 2009).

Various neuroimaging studies investigated the neural correlates of ToM. The experimental tasks typically used required the representation of other people's mental states to be correctly performed. Most of the studies used written stories, vignettes, or comic strips (Berthoz, Armony, Blair, & Dolan, 2002; Brunet, Sarfati, Hardy-Bayle, & Decety, 2000; Fletcher et al., 1995; Gallagher et al., 2000; Gobbini, Koralek, Bryan, Montgomery, & Haxby, 2007; Saxe & Kanwisher, 2003; Vogeley et al., 2001; Walter et al., 2004). Other studies required subjects to draw mentalistic inferences from physical stimuli such as photographs of the eye region of human faces (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999), or movement of simple geometrical shapes (Castelli, Happé, Frith, & Frith, 2000; Gobbini et al., 2007). Some studies focused on the interaction between an experimental subject and another agent (Gallagher, Jack, Roepstroff, & Frith, 2002; McCabe, Houser, Ryan, Smith, & Trouard, 2001; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004).

These studies show that various areas underlie ToM ability and contribute to support subjects' performance on ToM tasks. For example, the superior temporal sulci have been found to be involved in both the detection of agency (Frith & Frith, 2003) and the initial analysis of the stimuli corresponding to another person's biological motion, e.g., gaze direction; lip reading; and body, hand, and mouth movements (Allison, Puce, & McCarthy, 2000; Emery, 2000). The temporal poles, which are associated with mnemonic processes, supply the semantic and episodic context of the stimuli being elaborated; and the medial prefrontal cortex contributes to subsequent stimuli analysis to determine an explicit representation of our own and other people's mental states (Gallagher & Frith, 2003).

Recently, Saxe (2006) proposed an interpretation of neuroimaging data according to which the temporo-parietal junction, a region adjacent to the posterior part of the superior temporal sulcus, is specifically associated with the ability to represent the contents of mental states such as beliefs, while sub-regions of the medial prefrontal cortex support components of human social cognition such as the representation of triadic social interactions involved in shared attention and collaborative goals. In particular, in an fMRI study Saxe and Powell (2006) provided evidence that medial prefrontal cortex is broadly involved in representing socially and emotionally relevant information about another person, whereas the role of the left and right temporo-parietal junctions appeared to be restricted to the attribution of thoughts and beliefs to another person.

These latter findings could explain the observation provided by Bird, Castelli, Malik, Frith, & Husain (2004) of a single patient with extensive damage to the medial frontal lobes bilaterally presenting with profound executive deficits but no significant impairment in the ability to appreciate mental states. These authors proposed to a 62-year-old woman who suffered a rare form of bilateral anterior artery infarction a set of five ToM tasks: the picture sequences (Baron-Cohen, Leslie, & Frith, 1986) requiring the ability to arrange pictures into a predetermined order on the basis of characters' mental states; the strange stories (Happé, 1995) requiring the ability to use mental state understanding to make sense of non-literal utterances; the violation of social norms (Berthoz et al., 2002) involving the ability to decide if the protagonist of a social situation is embarrassed and if her/his behaviour is appropriate; the faux pas test (Baron-Cohen et al., 1999) in which is essential to understand whether in a social situation somebody said something that they should not have said; and finally the animations test (Abell, Happé, & Frith, 2000; Castelli et al., 2000; Castelli, Frith, Happé, & Frith, 2002) requiring the ability to attribute mental states to moving objects. Apart from a subscale of the violation of social norms task, patient's performance was within the normal range in all ToM tasks. Interestingly, Bird et al. (2004) underlined that, when considering the results of both the neuropsychological and the ToM tasks, patient's performance provides also evidence that executive functioning and ToM ability are dissociable. According to Bird et al. (2004), these findings call for caution against using functional imaging as the sole method for establishing cognitive neuroanatomy.

The evidence provided by Bird et al. (2004) is in disagreement with the idea of a single area underlying ToM and supports the hypothesis of a distributed neural network underlying ToM processing. In other words, evidence suggests that distinct areas might be specialised in processing distinct classes of social stimuli. In line with this explanation, in previous studies (Becchio, Adenzato, & Bara, 2006; Ciaramidaro et al., 2007; Walter et al., 2004) we demonstrated that the right temporo-parietal junction is sufficient for representing the mental states of people, as long as those people are acting outside social interaction, whereas the medial prefrontal cortex is necessary in understanding the intentions of other people who are specifically involved in social interactions, for example during communication.

Taken together, findings from a decade of neuroimaging studies strongly suggest that the medial frontal cortex (MFC), acting in concert with a limited set of other areas, is crucially involved in ToM ability. However, as the MFC makes up a large part of the human brain, it is essential that researchers and clinicians attempt to discriminate among the sub-areas that underlie different functions. In pursuing this aim, Amodio and Frith (2006) conducted a meta-analysis of findings on task-related neural activity in the MFC and developed a functional division model based on cognitive versus emotional processes (see Fig. 1). Specifically, the posterior region of the rostral MFC (prMFC) is activated by cognitive and action-monitoring tasks; the orbital MFC (oMFC) appears to be linked to the monitoring of task outcomes associated with either punishment or reward; and, more importantly for the aim of the

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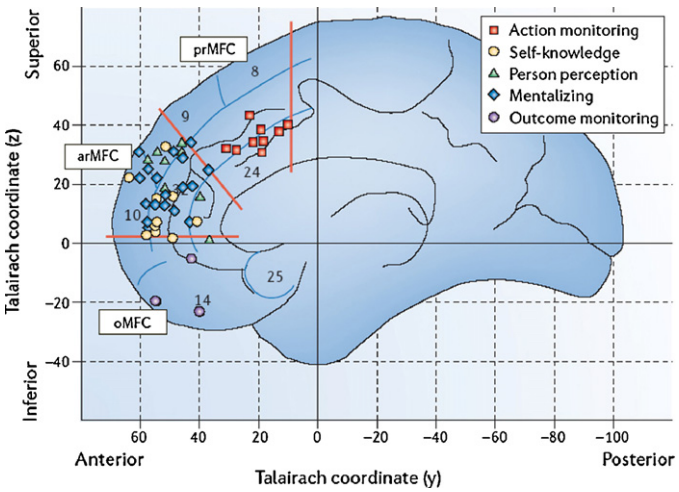

Fig. 1. Results from Amodio and Frith (2006) quantitative meta-analysis of MFC activation in social cognition studies. The figure maps MFC patterns of activation during action monitoring, social cognition, and outcome monitoring. The patterns of activation observed in the anterior rostral part of the MFC in mentalising tasks suggest a crucial role for this region in ToM ability (adapted from Amodio and Frith, 2006).

present work, the anterior region of the rostral MFC (arMFC) is activated by social cognition and mentalising (ToM) tasks.

Amodio and Frith (2006) underscored that different cognitive functions instantiated in the MFC form a systematic map: the authors suggested that the MFC is involved in determining future behaviour, and in particular, that it supports a general mechanism for the integration of complex representations. Interestingly, the more forward the brain area is, the more abstract these representations are, such that the most anterior region of the MFC (aMFC) is associated with metacognitive representations that enable us to reflect on the values linked to the outcomes of actions. Hence, at a neural level, the anterior part of MFC represents a crucial region supporting high level representations that play a key role in social behaviour and cognition, especially in ToM.

3. Anterior medial frontal cortex and the behavioural variant of frontotemporal dementia

Frontotemporal dementia (FTD) is the currently preferred term to describe non-Alzheimer type dementia affecting the frontal and/or temporal lobes (Brun et al., 1994; Hodges & Miller, 2001a, 2001b; Knibb, Kipps, & Hodges, 2006; Neary, Snowden, Northen, & Goulding, 1988). FTD exists in three variants characterised by three prototypical neurobehavioural syndromes and associated with characteristic patterns of cerebral atrophy (Lindberg et al., 2009; Schroeter, Raczka, Neumann, & Von Cramon, 2007): (1) *Progressive non-fluent aphasia* (PNFA), a disorder affecting expressive language characterised at the early stages by mainly left-sided alterations in the frontal and anterior temporal brain regions. PNFA patients show effortful speech production, phonologic and grammatical errors, word retrieval difficulties, and impairment in the syntactic aspects of language (Garrard & Hodges, 2000; Neary et al., 1998); (2) *semantic dementia* (SD), a severe naming and word comprehension impairment occurring in the context of fluent, effortless, and grammatical speech output. At the early stages of the condition, SD is principally characterised by alterations in the inferior and middle temporal gyri (Calabria, Cotelli, Adenzato, Zanetti, & Miniussi, 2009; Galton et al., 2001; Neary et al., 1998); and (3) *the behavioural or frontal variant* (bv-FTD), the present paper's focus of interest, in which the brain area mainly affected during the early stages is the MFC (Salmon et al., 2003; Schroeter, Raczka, Neumann, & Von Cramon, 2008).

The most common clinical manifestation of patients affected by bv-FTD is a profound alteration in personality and social conduct, characterised by inertia and loss of volition or, conversely, by social disinhibition and distractibility (Nakano et al., 2006; Neary et al., 1998; Peters et al., 2006; Rankin, Kramer, Mychack, & Miller, 2003; Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005). Only a minority suffer from depression (Bozeat, Gregory, Ralph, & Hodges, 2000; Levy, Miller, Cummings, Fairbanks, & Craig, 1996), and it is worth noting that the rather low incidence of depression in patients with bv-FTD may depend on the scarce insight that also characterises this condition (Gregory, McKenna, & Hodges, 1998; Miller et al., 2003; Neary et al., 1998). Indeed, a recent study reports specific anosognosia of these patients for personality and behavioural changes. Interestingly, the anosognosia is not related to a general executive dysfunction but rather to a perspective-taking disability and to an impaired processing of socio-emotional autobiographical information (Ruby et al., 2007). All of these behavioural symptoms are usually reported to clinicians by patient's family members (or friends) during clinical interviews and are identified through neuropsychiatric assessment (Hirono et al., 1999; Rosen et al., 2005; Williams, Nestor, & Hodges, 2005).

The pathological involvement of cerebral tissue is not limited to the frontal lobes only, as previously mentioned, but involves subcortical structures too, as well as parietal and temporal cortices (Broe et al., 2003; Diehl-Schmid et al., 2007). However, it is crucial to note two important points that reduce the role played by non-frontal areas in bv-FTD. Firstly, when one specifically considers the early stages of the condition only, "the neurodegenerative process is limited to the frontal lobes. During the progression of the disease, the pathological changes pass over the lobar borders and spread into the parietal and temporal cortices" (Diehl-Schmid et al., 2007, p. 42). Then, even if it is certainly true that at a given point in time the cerebral atrophy characterising bv-FTD patients spreads outside the frontal cortex up to more posterior regions, as long as one takes into account patients at the early stages of the condition, frontal lobe, and above all the ventromedial part of it, appears to be the single brain area where significant impairment is found in every bv-FTD patient (Salmon et al., 2003; Schroeter et al., 2008). Secondly, studies showing the pathological involvement of areas other than frontal ones (e.g., hippocampus, Barnes et al., 2007; Broe et al., 2003) typically used undifferentiated samples of FTD patients (e.g., bv-FTD patients, as well as patients affected by SD and PNFA, Barnes et al., 2007; or patients affected by SD, PNFA, motor neurone disease, and corticobasal degeneration, Broe et al., 2003). Thus, even if their results show the complex patterns of cerebral atrophy that *generally* characterise FTD syndromes, these results tell us rather little about the anatomical and functional profiles that *specifically* characterise bv-FTD patients. Indeed, functional neuroimaging studies investigating specifically the metabolism of various parts of frontal lobe in bv-FTD identified the anterior part of the MFC as the region mainly affected (Borroni et al., 2007; Salmon et al., 2003, 2006).

In detail, Salmon et al. (2003) identified the ventromedial frontopolar cortex as the specific region with metabolic impairment in each of the 29 bv-FTD patients examined (mean duration of illness = 2.5 years) in a multicentre study using a conjunction analysis of PET images. Furthermore, Salmon et al. (2006) identified the same impaired region in a multicentre study involving a cohort of 70 bv-FTD patients (mean duration of illness = 2.7 years). The results showed specific metabolic independence between anterior and posterior regions of the ventromedial prefrontal cortex, and between left and right subcallosal frontal regions. The authors identified the anterior region of the MFC as part of the first cluster explaining most of the variance in the metabolic images. Interestingly, a recent study linked the pathological involvement of this region to some neuropsychiatric features observed in the bv-FTD

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(Borroni et al., 2007). This study performed a voxel-based analysis of SPECT data in a cohort of 97 patients with frontotemporal lobar degeneration, including 41 patients with a diagnosis of bv-FTD (mean duration of illness = 3.1 years). Specific patterns of cerebral hypoperfusion were identified and linked to different behavioural symptom clusters. The aMFC hypometabolism was observed only in a specific subgroup of patients, characterised clinically by disinhibition and abnormal social conduct and consisting almost entirely of bv-FTD patients.

It is important to note that the functional metabolic studies discussed used an experimental condition similar to a rest state, i.e., functional images were typically acquired during quiet wakefulness with eyes closed. An important aspect that should be considered in functional studies is the role played by the aMFC in the so-called "default mode" brain network, that is, different typically deactivated brain regions that appear to be predominant in the absence of a demanding external task (Gusnard, Akbudak, Shulman, & Raichle, 2001). In neuroimaging literature, the aMFC deactivations are present in some baseline tasks and are attenuated during specific goal-directed behaviours (Raichle et al., 2001). Therefore, the hypometabolism noticed in the studies of our interest might depend more on the use of a resting state condition than on the presence of an actual frontal metabolic impairment in bv-FTD. In other words, the role of the aMFC in the bv-FTD cannot be entirely addressed without disentangling the process of social stimuli to the process of self-referential stimuli (Gusnard et al., 2001; Northoff & Bermpohl, 2004), task-independent thoughts (Binder et al., 1999; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003) or other social cognitive process that are related to resting state conditions.

In order to clarify this important point, it is crucial to observe that the pathological involvement of the aMFC in bv-FTD patients was also found in various morphometric studies, where the involvement of this region was noticed without taking into consideration any functional role of the frontal lobe, but only its morphology (Brambati et al., 2007; Perry et al., 2006). Then, due to the additional presence of marked frontal atrophy, it is extremely likely that the frontal hypometabolism invariably identified in bv-FTD mainly depends on the actual pathological involvement of its anterior part, and not on the experimental condition used. Indeed, in a study using tensor based morphometry to investigate the progression of grey matter atrophy in bv-FTD (Brambati et al., 2007), in the whole brain analysis the anterior cingulate/paracingulate gyri were the only regions that showed significant atrophy change over one year. Similar results were found by Schroeter et al. (2007) in a systematic and quantitative meta-analysis revealing what they called a 'triple dissociation', i.e., specific and distinct neural networks underlying each of the three variants of FTD (bv-FTD, SD, and PNFA). The bv-FTD involves the left and right anterior MFC, medial orbitofrontal cortex, right anterior insula, and anterior cingulate (see Fig. 2). Schroeter and colleagues linked these results with the somatic marker hypothesis (Damasio, 1996) and with risk-taking behaviour (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003), and suggested that this neural pattern may account for the clinical core diagnostic features of bv-FTD. Finally, the same authors conducted a recent meta-analysis of studies involving bv-FTD patients only (Schroeter et al., 2008). Their results identified the aMFC as the mainly affected region in a sample of 132 bv-FTD.

Overall, the results of the studies here reviewed suggest: (1) that the investigation of the different parts of the MFC specifically involved during the progression of the bv-FTD (such as the anterior parts) can lead to a better comprehension of the neurological bases of the symptoms that are, at a social level, typically observed in the everyday lives of bv-FTD patients, and (2) that there is a marked overlap between these parts of the MFC and the frontal regions recruited in the ToM neuroimaging studies described in the second paragraph.

4. Theory of mind in the behavioural variant of frontotemporal dementia

In recent years, it has been proposed that the personality changes and breakdown in social conduct frequently seen in bv-FTD may be at least partially explained by impairment in the ToM domain (Gregory et al., 2002; Kipps & Hodges, 2006). We take this view herein by considering it to be a productive way to examine the typical behavioural problems of bv-FTD patients and we review all of the studies investigating ToM ability in these patients.

The investigation of ToM ability in bv-FTD patients is commonly based on four tasks ordered here below in terms of developmental complexity and difficulty (Gregory et al., 2002).

The *First-order false belief test* is designed to assess an individual's ability to infer that someone has a (wrong) belief which differs

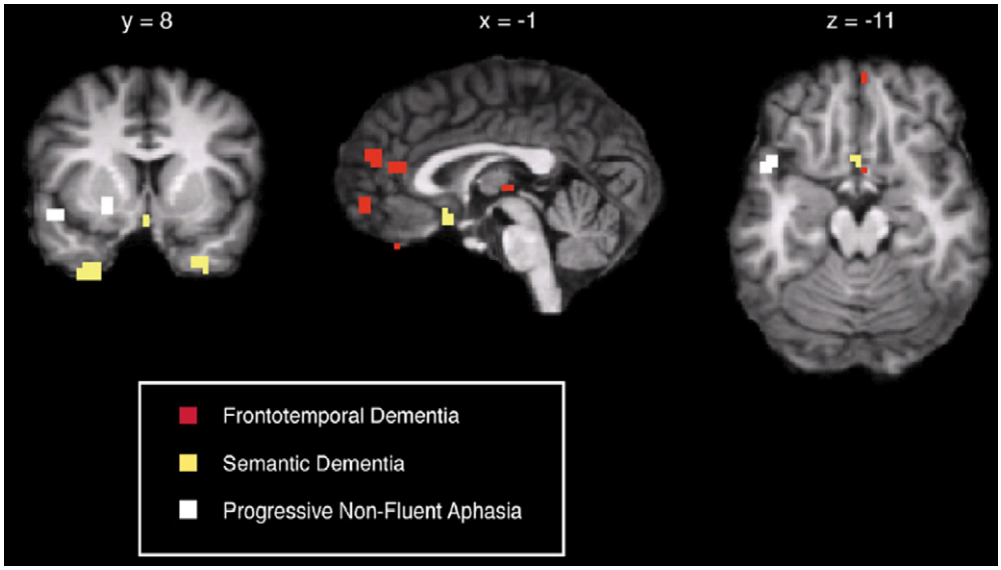

Fig. 2. Results from Schroeter et al. (2007) quantitative meta-analysis. The figure shows no overlapping regions for different dementia subtypes, and findings support previous notions classifying FTD as the frontal (or behavioural) variant of frontotemporal lobar degeneration (Perry & Hodges, 2000). The comparison of the anterior MFC clusters of cerebral atrophy with the patterns of activation mapped in Fig. 1 reveals strong overlapping with the brain regions activated in ToM studies. (Left side is left.)

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from the individual's own (true) belief (Baron-Cohen et al., 1985; Wimmer & Perner, 1983). In one version, the examiner tells a story accompanied by illustrations, in which two people (e.g., Sally and Anne) are in a room together. Sally places an object in a given location, witnessed by Anne. Sally then leaves the room, and Anne moves the object to another location while Sally is out of the room; Sally then returns to the room. Participants are asked a series of questions about Sally's beliefs concerning the object's location and other aspects of reality. Four-year-olds tend to succeed at this task, while younger children tend to fail (Wellman, Cross, & Watson, 2001; Wimmer & Perner, 1983).

The *Second-order false belief test* (Baron-Cohen, 1989; Perner & Wimmer, 1985) consists of a scenario regarding two characters (Sally and Anne again, for the sake of simplicity), which is recounted to and illustrated for participants. In a typical story, Anne sees Sally place an object in a specific location; Sally then leaves the room. While Sally is out of the room, Anne moves the object but, unbeknownst to Anne, Sally is peeking back into the room and sees the object being moved. Participants are then asked questions about Anne's beliefs concerning Sally's beliefs and other aspects of reality. This task, which children pass at about 6 or 7 years (Perner & Wimmer, 1985; Sullivan, Zaitchik, & Tager-Flusberg, 1994; Sullivan, Winner, & Hopeld, 1995), is more complex than the first-order task since here it is not sufficient to infer the thoughts of another person about the world, but is crucial to form beliefs about the content of others' minds (i.e., beliefs about beliefs).

In the *Faux pas test* a participant hears ten stories read aloud containing a social faux pas and ten control stories reporting a minor conflict, in which no faux pas is committed (Stone, Baron-Cohen, & Knight, 1998). After each story, participants are asked whether anyone said anything that they should not have said, i.e., to correctly identify the stories containing a faux pas. Children develop an appropriate understanding of social faux pas between 9 and 11 years (Baron-Cohen et al., 1999).

Lastly, the *Reading the Mind in the Eyes (RME)* is an adult and advanced test consisting in the presentation of photographs of the eye region of human faces (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Participants are required to choose among words that are printed on the page that the picture appears on, by using the criterion of which word best describes what the individual in the photograph is thinking or feeling. In order to pass this test participants have to recognise complex emotions and mental state, an ability that emerges around the time of adolescence (Baron-Cohen et al., 1997, 2001).

Recent studies have used these tasks to investigate ToM deficits in bv-FTD. One of the first studies conducted in this field examined the case of a 47-year-old man with a bv-FTD diagnosis and exhibiting severe antisocial behaviour (Lough et al., 2001). The first sign of his behavioural problems had been a dramatic decrease in his performance at work. He had then developed an obsession for obtaining as much money as he could to buy alcohol, cigarettes, and sweets. He had become agitated and impatient, and, from an interpersonal perspective, rude and discourteous. A computed tomography scan showed slight prominence of the lateral and third ventricles, and relative prominence of the frontal horns compared to the temporal ones. A three-dimensional magnetic resonance imaging (MRI) scan revealed marked atrophy in the frontal lobes (especially in the orbitomedial region) and in the temporal lobes bilaterally (particularly, in the pole and amygdala). The SPECT revealed significant bilateral hypoperfusion both in the orbitofrontal regions and in the anterior temporal lobes. Although a general neuropsychological assessment showed limited cognitive impairment, a ToM battery revealed that the patient failed both first- and second-order ToM tests and was unable to recognise a single faux pas, although he correctly answered the control questions. His ability to detect emotional states (measured via the RME test) was intact. Altogether, this study found a deficit in ToM ability independent of the level of executive functions assessed using the Wisconsin Card Sorting Test (WCST, Heaton, Chelune, Talley, Kay, & Curtis, 1993), the FAS version of the verbal fluency (Thurstone & Thurstone, 1962), and the Behavioural Assessment of Dysexecutive Syndrome (Wilson et al., 1996). Similar results were found by Lough and Hodges (2002) in a further single-case study. These authors investigated the performance of a 57-year-old man presenting with marked behavioural symptoms such as personality changes, disinhibition, decline in self-care, and drinking problems. He had also developed paranoid ideation and begun to compulsively check the doors and windows in his home. He had undergone general neuropsychological assessment showing limited cognitive impairment. An MRI scan revealed marked atrophy in the orbitofrontal regions, with a less marked involvement of the dorsolateral frontal cortex, anterior temporal regions, and amygdala bilaterally. The SPECT showed considerable hypoperfusion of the frontal lobes bilaterally. The patient was administered the previously described ToM tasks and interestingly he showed a severely impaired performance on all of them with a clear dissociation between executive functions and ToM ability.

The first study examining the ToM ability in a group of bv-FTD patients was conducted by Gregory et al. (2002) who compared the performance of these patients with the performance of Alzheimer's disease (AD) patients and healthy controls. All of the participants underwent general neuropsychological assessment, and caregivers completed the Neuropsychiatric Inventory (Cummings et al., 1994), which detects significant behavioural symptoms. The bv-FTD patients obtained higher scores on this measure than the AD patients did, confirming the marked behavioural and interpersonal problems that are typical of this clinical condition. The authors also focused on evaluating frontal lobe atrophy in two specific regions: the ventromedial and the dorsolateral prefrontal cortices. Most of the patients showed a more severe pathological involvement in the former, indicating an early stage of disease. Lastly, all participants were administered the previously described ToM tasks. Bv-FTD patients performed poorly on all ToM tasks and the independence of traditional executive functions tests (assessed using the WCST and the FAS) and ToM tasks was observed.

For the aim of the present work, it is important to underline the strong relation that Gregory et al. (2002) found among high neuropsychiatric interview scores (i.e., marked presence of behavioural symptoms), impaired performance on all ToM tasks, and location and severity of frontal lobe atrophy in bv-FTD patients, compared to both AD patients and healthy controls. Specifically, the observed atrophy was located mainly in the ventral MFC (but the dorsolateral prefrontal cortex was also involved), and the results highlighted a clear association between ToM impairment and the degree of ventromedial frontal atrophy.

A more recent study (Torralva et al., 2007) investigated ToM capacities and decision-making abilities in a group of bv-FTD patients at early/mild stages of the disease (duration of illness = 2–4 years). All underwent neurological, neuropsychological, and neuropsychiatric assessment as well as MRI and SPECT. Frontal lobe atrophy and/or hypoperfusion were observed. Specifically, although all patients received different atrophy scores, none were in the normal range. Furthermore, all of the patients presented marked changes in personality and social behaviour, as corroborated by caregivers. The RME and the faux pas tests were administered, as well as the Iowa Gambling Task, a test of affective decision-making (Bechara, Damasio, Damasio, & Anderson, 1994). The results showed that bv-FTD patients' performances were significantly worse than controls on both the faux pas and the RME tasks. A strong correlation between scores on the two ToM tasks

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also emerged, whereas no associations between ToM performance and decision-making tasks were found.

Three other studies have investigated social cognition abilities in bv-FTD patients using ToM tasks different from the ones described above. Lough et al. (2006) used ToM cartoons (adapted from Corcoran, Cahill, & Frith, 1997) based on different types of cartoon jokes: physical jokes involving physical events, and ToM jokes requiring an understanding of characters' mental states. ToM stories describing naturalistic social situations (Happé, 1994) were also used. Overall, the results showed that ToM was defective in bv-FTD patients and that these patients were also impaired in other components of the social cognition domain. Interestingly, although executive functions (as measured by the Hayling and the Brixton tests; Burgess & Shallice, 1997) were impaired, ToM performance was found to be independent of them.

The last two studies we review in this section are the only ones showing a correlation between ToM and executive function tests. Snowden et al. (2003) investigated the ability to interpret social situations (such as humour appreciation, deception, bluff, and double bluff) and attribute mental states to others in patients with bv-FTD and Huntington's disease (HD). To this aim the authors used single cartoon, cartoons pairs, story comprehension (Happé, Brownell, & Winner, 1999), and judgment of preference tasks (Baron-Cohen, Campbell, Karmiloff-Smith, Grant, & Walker, 1995). Compared to healthy controls, the performance of bv-FTD patients was severely impaired on all of the ToM tasks, whereas the HD group showed milder impairment in interpreting cartoons and stories and normal preference judgements. The authors paid particular attention to bv-FTD patients' performance on the judgment of preference task. In this task participants merely point to one of four pictures that a cartoon face prefers, preference being determined by direction of eye gaze. While the other ToM tasks used in the study are relatively demanding in terms of cognitive load, this task is substantially undemanding and requires no active mental manipulation or integration of information. Interestingly, bv-FTD patients failed to ascribe preference ("Which one does he like?") but had no difficulty in reporting direction of eye gaze ("Which one is he looking at?"). As these two sub-tasks differ in terms of mental state attribution but not in terms of cognitive load required, the authors suggest that the performance differences shown by the bv-FTD patients provide evidence for a specific ToM impairment. Persuasively, Snowden and colleagues argue that, while it is reasonable to suppose that executive functions generally contribute to test performance, their impairments impact only in a secondary way on the ToM tasks and may also mask specific deficits in mental state attribution in bv-FTD patients.

Furthermore, in bv-FTD patients the relationship between performance on ToM and standard executive tests was relatively modest and not systematic across tasks. In particular, only a correlation between the cartoon task and the executive tests administered (i.e., the WCST, the category and letter fluency tests) was found, whereas no correlations emerged between the other ToM tasks and the executive tests. Compared to Gregory et al. (2002)'s work, Snowden et al. (2003) found a more compromised performance on executive functions tests. They explicitly interpreted these results as a consequence of a pathological involvement of dorsolateral frontal structures typically associated with a more advanced stage of illness in their sample.

The crucial role played by the patients' stage of illness is also highlighted by a recent work conducted by Eslinger et al. (2007). These authors were interested in studying the ability to solve standardised social dilemmas in patients with FTD. They were divided into two subgroups: patients with social and executive impairments (SOC/EXEC) and patients witsh progressive non-fluent aphasia or semantic dementia (APH). Two tasks were presented to investigate the social cognitive domain. One was a cartoon prediction task (O'Sullivan & Guilford, 1965) requiring participants to identify the thoughts, feelings, and intentions of cartoon characters involved in social situations, and to choose the most likely subsequent event from three different options. The other task presented vignettes depicting characters involved in social situations (Winner, Brownell, Happé, Blum, & Pincus, 1998) and asked participants to answer to questions requiring the attribution of mental states to the characters. Interestingly, impaired social judgments in SOC/EXEC patients were associated with ToM and cognitive flexibility deficits (assessed with the visual–verbal test, Feldman & Drawgow, 1960) and were related to right hemisphere cortical atrophy, which was localised mainly in the orbital frontal and superior temporal regions. The performance impairment of APH patients, conversely, was found to be less frequent and less severe. More precisely, APH patients showed an impaired performance on the cartoon prediction task, even if of a lesser degree than SOC/EXEC patients.

To the aim of our study it is worth noting that both the samples involved in the Eslinger et al. (2007) and in the Snowden et al. (2003)'s works are the only ones in which the bv-FTD patients' performance on the Mini-Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975) was below the cut-off of 24/30. In all of the other studies here reviewed the cut-off was in the normal range. Thus, Eslinger et al. (2007) and Snowden et al. (2003)'s findings strongly suggest that correlations between executive functions and ToM ability tend to emerge only in samples including patients in a more advanced stage of illness, when atrophy has spread up to the dorsolateral frontal cortex.

In brief, all of the above-cited studies examined bv-FTD patients and reported the presence of a breakdown in social conduct and dramatic personality changes, accompanied by a significant and specific decay, at a cognitive level, in ToM capacity (see Table 1). In addition, the structural and functional neuroimaging findings reported herein have shown the pathological involvement of the ventral MFC and less marked involvement of the dorsolateral frontal cortex and temporal regions, at least in the early stages of the disease.

5. Discussion

The bv-FTD domain represents a particular challenge for researchers and clinicians, due to the absence of universally accepted biological markers (Robillard, 2007), its insidious onset, and ambiguous clinical features, which frequently render precise diagnosis difficult (Gregory et al., 2002; Lough & Hodges, 2002; McMurtray et al., 2006). A better comprehension of this clinical condition can be achieved by considering the neural, cognitive, and social levels as equally important and integrated aspects. Our examination was based on the question of whether the neuropsychiatric profile of bv-FTD patients may be at least partially explained by a deficit in the ToM domain.

Neuroimaging studies in healthy participants show the crucial role of the anterior parts of the MFC in ToM tasks performance. We linked these findings with the ones emerging from studies indicating that in bv-FTD hypometabolism and volume loss follow a well-defined progression order, which in the early stages compromises mainly the aMFC areas. More precisely, the results of the studies reviewed in the present paper strongly suggest that cerebral atrophy and glucose hypometabolism are typically more pronounced in the ventromedial frontal regions than in the dorsolateral regions (Salmon et al., 2003, 2006). Indeed, Salmon et al. (2003) found that the ventromedial frontopolar cortex was the single area pathologically involved in all of the patients recruited, irrespective of age, sex, disease duration, or degree of severity of dementia. Moreover, both Schroeter et al.'s meta-analyses (2007,

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Table 1
Bv-FTD studies including theory of mind tasks.

Authors, published	Sample (*n*)	Mean age (years) (SD)	Sex m/f	Brain imaging techniques	Neuropsychological assessment	ToM tasks	Main ToM results
Lough et al. (2001)	single-case bv-FTD	47	1/0	CT MRI SPECT	Relatively intact general neuropsychological and executive functions	First-order FBT Second-order FBT Faux pas test RME test	Performance impaired on first-order FBT, second-order FBT, and Faux pas Normal performance on RME test. ToM deficit independent of level of executive functions
Gregory et al. (2002)	19 bv-FTD 12 AD 16 HC	58.6 (6.9) 66.5 (8.9) 57.1 (5.1)	16/3 6/6 8/8	CT or MRI SPECT	Bv-FTD mildly impaired on executive functions tests, although some patients obtained normal range scores	First-order FBT Second-order FBT Faux pas test RME test	Bv-FTD patients impaired on all ToM tasks. AD patients performed poorly on second-order FBT task. Performance on ToM tasks was largely independent of frontal measures used
Lough and Hodges (2002)	Single-case bv-FTD	57	1/0	MRI SPECT	Within normal range on traditional executive functions tests	First-order FBT Second-order FBT Faux pas test RME test	Poor performance on all ToM tasks. ToM appears to dissociate from frontal executive functions
Snowden et al. (2003)	13 bv-FTD 13 HD 18 HC	60 (7) 50 (7) 49 (23)	9/4 5/8 8/10	MRI SPECT	Bv-FTD patients showed frontal executive impairment. Patients were in later stage of disease and had lower mean MMSE and WCST scores than patients in other studies	ToM cartoons and stories	Bv-FTD patients performed severely poor on ToM tasks. Bv-FTD group more severely affected than HD group
Lough et al. (2006)	18 bv-FTD 13 HC	61.1 (6.7) 57 (9.1)	16/2 9/4	CT or MRI	Bv-FTD patients showed impairment on Hayling and on Brixton executive tasks	ToM cartoon jokes ToM stories	Bv-FTD patients performed poorly on ToM tasks. Findings suggest a supporting role of executive functions in both the attribution of mental states and control conditions of ToM tasks. A dissociation between attribution of mental states and executive functions was observed

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Table 1 (*Continued*)

Authors, published	Sample (*n*)	Mean age (years) (SD)	Sex m/f	Brain imaging techniques	Neuropsychological assessment	ToM tasks	Main ToM results
Eslinger et al. (2007)	12 FTD (SOC/EXEC) 14 FTD (APH) 17 HC	66.17 71.92 75.07	NA NA NA	MRI	In the only executive task administered (visual–verbal test) the FTD (SOC/EXEC) patients showed modest difficulty, as compared with FTD (APH) patients	ToM vignettes	FTD (SOC/EXEC) patients performed poorly on ToM task. Deficits in FTD (APH) were less severe and were infrequent
Torralva et al. (2007)	20 bv-FTD 10 HC	67.2 (8.1) 63.5 (5.8)	11/9 4/6	MRI SPECT	Bv-FTD patients had normal performance on Raven matrices, digits backwards, trail B, and perseverative errors on WCST. Patients were impaired for letters and number ordering (WAIS), number of categories achieved on WCST and frontal assessment battery	Faux pas test RME test	Bv-FTD patients performed poorly on the ToM tasks

The order is chronological.
ACE = Addenbrooke's cognitive examination; AD = Alzheimer's disease; Bv-FTD = Behavioural variant of frontotemporal dementia; CT = Computed tomography; FBT = False belief task; FTD (APH) = Subgroup of FTD patients with progressive non-fluent aphasia or semantic dementia; FTD (SOC/EXEC) = Subgroup of FTD patients with a social and executive disorder; HC = Healthy controls; HD = Huntington's disease; MMSE = Mini-Mental State Examination; MRI = Magnetic resonance imaging; RME = Reading the mind in the eyes test; SPECT = Single-photon emission computed tomography; ToM = Theory of mind; WAIS = Wechsler adult intelligence scale; WCST = Wisconsin Card Sorting Test.

2008) indicate specific neural clusters for the bv-FTD that do not overlap with the neural clusters that characterise other FTD variants. Both studies indicate a region of the frontomedian structures, the aMFC, as the mainly affected region in bv-FTD patients. These data fit well with our aim to achieve a higher degree of precision, by comparing a detailed localisation of frontal atrophy during the degenerative course with what is known about the functional division of the MFC.

Evidence in accordance with this aim arises from the recent meta-analyses conducted by Schroeter et al. (2007, 2008) and Amodio and Frith (2006) (see Figs. 1 and 2). Schroeter et al. (2007) found a 'triple dissociation' among the neural correlates of bv-FTD, SD, and PNFA. Specifically, they found that the neural patterns underlying these different forms of dementia do not overlap. We emphasise, conversely, that a full overlap in the anterior regions of the rostral MFC emerges between the frontal area involved in the ToM processing and the neural atrophy characterising bv-FTD. Schroeter et al. (2007) meta-analysis clearly showed that the two areas most affected in bv-FTD are the left and the right anterior MFC (Talairach coordinates: −5 49 21 and 1 55 −3). Indeed, these two areas alone make up over 75% of the brain volume affected in bv-FTD. Even more importantly, the coordinates reported by the authors were all located in the anterior part of the rostral MFC, the brain area identified by Amodio and Frith (2006) as being crucial in all of the ToM neuroimaging studies they reviewed (see the Talaraich coordinates mapped in Fig. 1). Although at this point in time it is not possible to *precisely* match the regions subserving different functions with an *exact* pattern of regions involved in the progression of the bv-FTD disease, these data suggest that it is at least possible to *correlate* patients' patterns of social and behavioural problems with the frontal areas that are crucial in supporting the ToM ability and that are primarily involved in the neurodegenerative process.

Bv-FTD patients show a combination of severe modification in social conduct, in association with dramatic and increasingly severe personality and social behaviour changes. As summarised in Table 1, research findings suggest that bv-FTD patients tend to perform more poorly than other dementia patients and healthy controls do on ToM tasks and that the social abilities tapped by these tasks are typically compromised in bv-FTD patients. Their dramatic behavioural problems may therefore be at least partially explained by an acquired incapacity to critically reflect upon and choose an appropriate way of behaving, among the various options available, in a given social context. According to Snowden et al. (2003), traditional neuropsychological tests are not sufficiently sensitive to capture and identify most of the behaviour changes shown by bv-FTD patients in their daily lives. This type of insensitivity is mainly due to two aspects that typically characterise traditional tests, i.e., constrained situations and impersonal involvement, aspects that are diametrically opposed to everyday life situations, which conversely are open-ended and require self-generated organisation in the context of cognitively demanding social interactions. Thus, it is not by chance that Mioshi et al. (2007) recently found that bv-FTD has a devastating effect, more than SD and PNFA, in everyday life social situations.

Marked difficulties in appropriately performing ToM tasks emerged in all of the studies examined herein, a finding that strongly supports the proposal that they be used systematically in bv-FTD assessment during the early stages of the diagnostic process. Anyhow, it is worth underlining that ToM tasks used in the studies we reviewed are not equivalent and they might draw on various cognitive functions that are not captured in the clinical tests of executive functions (McKinnon & Moscovitch, 2007). As persuasively stated by Apperly, Samson, & Humphreys (2005), in the current state of neuropsychological research there is no definitive evidence for domain specificity of ToM, at least concerning the

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belief reasoning assessed with the false belief tasks. In all probability, false belief tasks are not well suited to study the key issue of the relationship between ToM and executive functions (Bloom & German, 2000) and future works should make use of tasks able to disentangle the specific contribution of ToM processing from the contribution of other processing resources (e.g., attention and working memory).

Another aspect that should be considered in future functional studies with bv-FTD patients is the role of the aMFC in the rest state, i.e., in the default-mode network. Rather than a passive network, it has been suggested that it likely mediates active cognitive processes as self-monitoring, self-referential process and self-generated thoughts (Gusnard, 2005; Raichle et al., 2001). Further functional studies, therefore, have to take into account that the resting state provides a non-optimal baseline for assessing ongoing activity in aMFC (Gusnard & Raichle, 2001; Stark & Squire, 2001). This suggestion is relevant for future studies aiming both at clarifying the role of the aMFC in social cognition and at investigating the role of aMFC in the social problems of bv-FTD patients.

6. Conclusions

The main aim of our paper was to consider the specific contribution of ToM deficits in the clinical presentation of bv-FTD, by analysing the relevant evidence that comes from neuroimaging, neuropsychological and ToM studies. We thus did not aim at highlighting that ToM problems explain all of the clinical features of bv-FTD, but more modestly we aimed at providing convergent and substantive evidence that ToM deficits invariably characterise this condition. Based on a social cognitive neuroscience perspective, we proposed a complex way of examining bv-FTD by taking the neural, cognitive, and social levels into due account. Studies pertaining to each of these levels can provide important data on one specific aspect of this difficult-to-diagnose clinical condition, but we strongly support the view that only a careful consideration of all of these levels can lead to a better understanding of its currently controversial nature. Indeed, the specificity of impairment observed in bv-FTD represents an important opportunity for clinicians and researchers to apply a multi-level perspective, given the contemporaneous presence of progressive degeneration in specific neural structures (the neural level), impairment of specific cognitive abilities but not of others (the cognitive level), and a wide range of behavioural problems leading to dramatic interpersonal difficulties in daily life (the social level). In other words, the essential feature of this condition including neural, cognitive, and social levels is its *dynamism*, i.e., that a patient's situation reflects a particular combination of these levels at a given point in time, thereby rendering each neuropsychological and neuropsychiatric evaluation 'reliable' for that particular moment only.

Literature to date suggests both the crucial role played by specific parts of the MFC in supporting ToM ability and the pathological involvement of specific regions of this frontal area during the course of bv-FTD. It can be reasonably assumed that the brain regions that are critically involved in ToM capacities are the same as those that are compromised in the early stages of bv-FTD. Hence, the question remains: given the above-described premises, can the neuropsychiatric profile of bv-FTD patients (their most important clinical feature) be at least partially explained by a deficit in ToM domain? Promising evidence for an affirmative answer to this question is now available. Researchers and clinicians should therefore consider the implications of these findings by including a careful ToM assessment into the diagnostic procedures and implementing effective behaviour management strategies when working with bv-FTD patients.

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