

THEORY OF MIND ABILITIES IN NEURODEGENERATIVE DISEASES: AN UPDATE AND A CALL TO INTRODUCE MENTALIZING TASKS IN STANDARD NEUROPSYCHOLOGICAL ASSESSMENTS

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Abstract

There is fast-growing interest in the study of Theory of Mind (ToM) abilities in neurodegenerative diseases. In a previous work, we reviewed all the evidence of altered ToM abilities in patients with neurodegenerative diseases in the literature published until then. In the present paper, we extend that analysis by integrating our conclusions with the most updated evidence that is now available. This new analysis allows for a clarification of some pending questions, such as at which stage ToM deficits begin to appear in dementing disorders, what is the relationship between executive functioning and ToM abilities in patients with Parkinson's disease, and how can ToM tasks help clinicians to discriminate between different neurodegenerative disorders. Furthermore, we now provide the first review of all articles on ToM abilities in patients with multiple sclerosis. The data discussed here strongly suggest overall that a neuropsychological assessment of patients with neurodegenerative diseases should routinely include an accurate investigation of ToM abilities. Increasing evidence has shown that different ToM tasks may help clinicians in the diagnostic process and caregivers in understanding the behavioural problems that are often shown by their suffering relatives.

Key words: Alzheimer's disease, essential tremor, executive functions, frontotemporal dementia, Huntington's disease, mild cognitive impairment, multiple sclerosis, neurodegenerative diseases, Parkinson's disease, prefrontal cortex, progressive supra-nuclear palsy, Theory of Mind

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1. Introduction

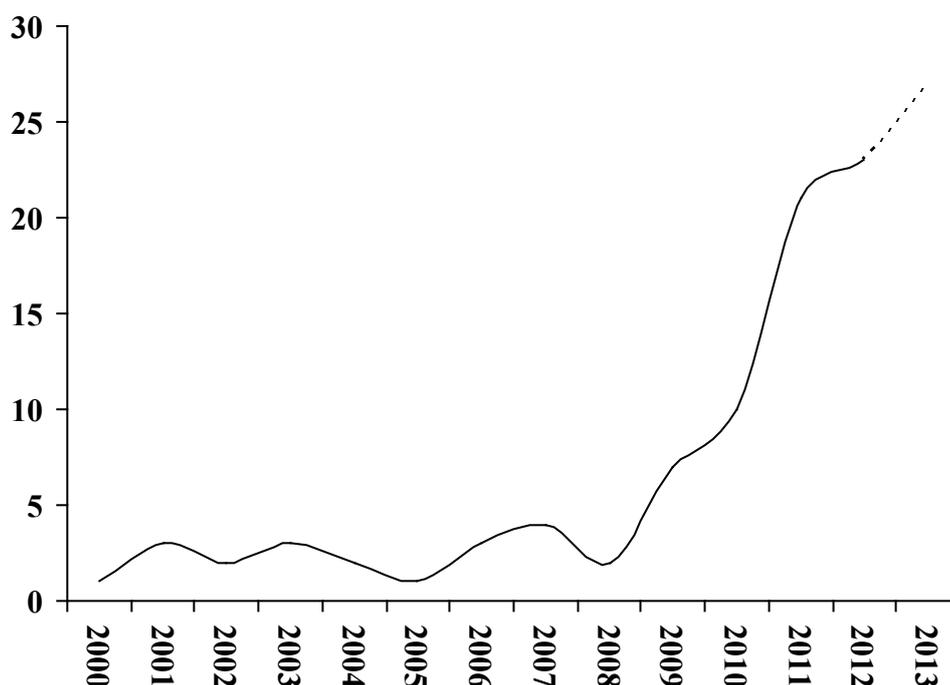
Over the last few years, researchers have started dedicating ever greater and systematic attention to investigating the cognitive and neural processes that underlie the ability to attribute mental states, such as intentions and beliefs, to others in order to understand and predict their behaviour (theory of mind, ToM) and the neuropsychological and neuropsychiatric consequences of deficits of these complex processes. For evidence of the scientific world's growing interest in the topic of the present paper, we only need to consider the increased number of theoretical and experimental studies on the role of the ToM in neurodegenerative diseases published in the last few years, as confirmed by a bibliographical search conducted in July 2013 (see the graph shown in **figure 1**).

ToM abilities have been investigated in several neuropsychiatric disorders, such as schizophrenia

(e.g., Walter et al. 2009), anorexia nervosa (e.g., Adenzato et al. 2012), depression (e.g., Wang et al. 2008), borderline personality disorder (e.g., Arntz et al. 2009), and different non-autistic psychiatric disorders of childhood and adolescence (e.g., Poletti and Adenzato 2013). Lesion studies (Shamay-Tsoory and Aharon-Peretz 2007, Lee et al. 2010, Roca et al. 2011) and neuroimaging and transcranial magnetic stimulation studies (Walter et al. 2004, Ciaramidaro et al. 2007, Kalbe et al. 2010, Bara et al. 2011, Enrici et al. 2011) have demonstrated that ToM abilities are critically based on a widely distributed neural network that includes the prefrontal cortex, precuneus, posterior superior temporal sulci, and neighbouring but distinct regions of the temporo-parietal junction.

Last year, Poletti, Enrici, Adenzato (2012) reviewed all the evidence of altered ToM abilities in patients with neurodegenerative diseases in the literature published until then. In the present paper, we extend their analysis

Figure 1. Experimental and theoretical articles published on the topic “ToM in neurodegenerative diseases” between 2000 and 2013. Source: Scopus and Thomson Reuters – Web of Knowledge



by integrating their conclusions with the most updated evidence that is now available. The studies that were included were identified through searches in the Thomson Reuters Web of Knowledge, PubMed, and Scopus electronic databases. Only studies in English and reporting data on performances in ToM tasks by patients who were diagnosed according to accepted consensus guidelines for clinical or pathological diagnoses were included. The final search for this review was conducted in July 2013. The keywords used for the search were Alzheimer’s disease, Frontotemporal Dementia, Parkinson’s disease, Huntington’s disease, Amyotrophic Lateral Sclerosis, Dementia, Multiple Sclerosis, and Neurodegenerative disease, and these were combined with each of the following terms: Mentalizing, Mind-reading, and Theory of Mind. In the present work, the articles that met the criteria for inclusion and were published after publication of the review by Poletti et al. (2012) are discussed.

This new analysis allows for a clarification of some pending questions, such as at which stage ToM deficits begin to appear in dementing disorders, what is the relationship between executive functioning and ToM abilities in patients with Parkinson’s disease, and how can ToM tasks help clinicians to discriminate between different neurodegenerative disorders. Furthermore, we now provide the first review of all articles on ToM abilities in patients with multiple sclerosis.

2. Theory of Mind in Multiple Sclerosis

Multiple Sclerosis (MS), a chronic inflammatory disease of the central nervous system, is associated with diffuse demyelination of the white matter. Most patients are diagnosed between 20 and 50 years of age, and women are affected two to three times more often than men (Prakash et al. 2008). In their review, Poletti et al. (2012) omitted this disease from analysis as this neuropathological condition has been

traditionally considered exclusively as an immune-mediated demyelinating disease of the central nervous system; however, increasing evidence now indicates that neurodegenerative processes play a critical role, justifying the inclusion of MS in the present work.

The term *neurodegeneration* has now come to be widely accepted in MS research, although its implication is slightly different from that in the context of the classical neurodegenerative diseases (Stadelmann 2011). Specifically, as proposed by van Noort et al. (2012), both immune-mediated and neurodegenerative processes play a role in the pathogenesis of MS. According to these authors, the link between these two seemingly unrelated elements is the neurodegeneration-induced accumulation of the small heat shock protein HSPB5 in preactive MS lesions, which are small foci with innate immune activity present in normal-appearing central nervous system tissue in patients with MS. This accumulation, in turn, can provoke a destructive local adaptive response of the otherwise normal immune system. In addition to neurological deficits, patients with MS show cognitive deficits with current prevalence rates ranging from 30% to 70% (e.g., Rao et al. 1991). The cognitive domains that are more affected are executive functions, memory, information processing speed, and attention (Bobholz and Rao 2003, Chiaravallotti and DeLuca 2008, Borghi et al. 2013). Cognitive dysfunction may present at an early stage or in patients who are not yet physically disabled (Glanz et al. 2007), and information processing speed may be the domain most sensitive to the impact of MS on cognitive functioning over time (Denney et al. 2008).

The first study to assess ToM abilities in MS was performed by Julie Henry and colleagues (2009). These authors used the Reading the Mind in the Eyes (RME) task to index ToM in a sample of 27 patients with MS. RME assesses affective ToM through the presentation of photographs of the eye regions of human faces (Baron-Cohen et al. 2001). Participants are required to

choose which word best describes what the individual in the photograph is thinking or feeling. Compared to healthy controls, patients with MS present deficits on the RME task. Interestingly, in these patients, correlations between performance on the RME task and performances on tests that assess phonemic and semantic fluency were found, suggesting a possible role of dysfunctional executive control processes in the poor performance on the RME. Similar ToM deficits on the RME test were found by Banati and colleagues (2010), and these deficits were detected even when multiple logistic regressions were applied after adjusting for the confounding factors of depression and anxiety. Furthermore, these authors examined whether physical disability and disease duration impacted ToM in patients with MS. To this end, they used in addition to the RME also the Faux pas recognition (FPR) task; this task assesses both the cognitive and affective components of ToM. In the FPR task, the participants hear stories that are read aloud; test stories contain a social faux pas, and control stories report a minor conflict but no faux pas (Stone et al. 1998). After each story, the participants are asked whether anyone said anything that they should not have said in order to identify the stories containing a faux pas (the affective component). When a faux pas is detected, further clarifying questions are proposed in order to evaluate the understanding of the mental states of the agents that are involved in the stories (the cognitive component). Banati and colleagues found that deficiencies on the RME test were not related to disability, but the more disabled subgroup, which was estimated with the Expanded Disability Status Scale (EDSS), was impaired in recognizing faux pas. In addition, ToM deficits were more severe in patients with long disease courses, suggesting that disease duration and increasing disability are both accompanied by a decline in social cognition. It is worth noting that the patients with MS that were tested by Banati and colleagues had mild or moderate disabilities, and, thus, ToM deficits seem to occur in the early stages of the disease.

Impaired performances on the ToM tests in the early stages of MS disease were recently reported by Kraemer and colleagues (2013). These authors tested ToM in a homogeneous cohort of 25 young and non-disabled patients in early stages of relapsing-remitting MS with the Movie for the Assessment of Social Cognition (MASC, Dziobek et al. 2006), which is a test requiring participants to attribute mental states to movie characters in a naturalistic setting. The early stage of the disease was defined as a short time (less than 24 months) since diagnosis and a very low EDSS score (2 or lower, i.e., from minimal disability in one functional scale to normal neurological status). Kraemer and colleagues reported a significantly greater reduction in ToM performance of the patients compared to controls. Furthermore, a positive correlation between the deficits in ToM performance and the results on the interference task of the Stroop test (a measure of executive function) was found.

In an effort to better understand the contribution of cognitive functions to the ability to infer mental states in patients with MS, Ouellet and colleagues (2010) classified their sample group of 41 patients into cognitively impaired (MS-) and cognitively intact (MS+) subgroups, according to their neuropsychological tests results. To this end, these authors administered a set of ToM tests, including the FPR task, the Strange Stories task (Happé 1994), and a video task that measured, in a naturalistic way, a participant's ability to interpret the mental states behind an explicit message conveyed by

a character. Their results demonstrated that compared to patients having MS without cognitive impairments, those with mild to moderate cognitive deficits are more prone to have trouble in attributing mental states to others. Interestingly, there were no differences on the ToM tasks between the MS+ patients and healthy controls, supporting the hypothesis that the contributing factor in the ToM impairments shown by the MS patients was the cognitive deficits, and not the MS *per se*.

ToM deficits that occur in patients with MS independently of their well-known neuropsychological deficits have been found in two studies (Henry A. et al. 2011 and Pöttgen et al. 2013). In the study by Audrey Henry and colleagues (2011), first- and second-order ToM tests and the FPR test were used. Their results showed that compared to healthy participants, patients with relapsing-remitting MS obtained significantly lower scores on all ToM task global scores. Nevertheless, in the FPR test, they found no significant differences in the individual questions. Despite the finding that MS patients did not understand that the faux pas was not intentional, they correctly detected that a faux pas occurred (affective component). According to the authors, patients with MS may encounter difficulty while attempting to infer epistemic mental states (cognitive ToM), but they may be more effective when inferring affective mental states (affective ToM). Finally, the three ToM task global scores were not found to be correlated with demographic or clinical characteristics, including duration or severity of disease, or with any cognitive dimensions that were explored, including executive functioning. Consistent with these results, Pöttgen et al. (2013) recently found ToM deficits in a group of 45 patients with MS on the MASC task. These deficits occurred independent of the neuropsychological deficits and were detected in patients during the early stages of the disease.

Taken together, these reviewed studies indicate impaired performances of patients with MS, especially, those with cognitive impairments, on the ToM tasks. Due to the inconsistent results concerning the relationships between neuropsychological tests and ToM tasks, it remains unclear if ToM impairments in MS are secondary to the neuropsychological deficits or occur independently. Thus, although these studies should be interpreted with caution because of their often small sample sizes, the results presented here clearly show that impairments in ToM abilities can emerge in the early stages of MS disease and that these impairments may contribute to relevant everyday problems in interpersonal relationships in these patients. These ToM impairments are important for managing and caring for patients with MS.

3. Theory of Mind in Amnesic Mild Cognitive Impairment and Dementing Disorders

Amnesic mild cognitive impairment (aMCI) is a risk factor for the development of Alzheimer's disease (AD) (Ahmed et al. 2008, Sperling et al. 2011). Patients with aMCI typically present a clinical picture of subjective cognitive complaints of isolated deficits of memory in the absence of dementia and of adequately preserved functional activities (Petersen et al. 2009, Landau et al. 2010), even if mild executive deficits involving response inhibition, set-shifting, planning and working memory may be present (Traykov et al. 2007, Brandt et al. 2009). From a neuropathological point of view, aMCI is characterized by early medial temporal atrophy

and milder signs of prefrontal neurodegeneration, which are presented as hypometabolism and cortical thinning (Chang et al. 2010, Han et al. 2012, Nishi et al. 2010).

Because of its often elusive clinical nature, aMCI has been ignored by researchers involved in the study of ToM abilities in patients with neurodegenerative diseases, for a long time. Recently, this lacuna has been filled by four studies. The first study that assessed ToM abilities in this population (Baglio et al. 2012) reported impaired performances on two second-order false belief tasks and preserved performance on the RME task in 16 patients with aMCI compared to controls. However, this apparent dissociation between a preserved affective ToM, as assessed by the RME task, and an impaired cognitive ToM, as assessed by false belief tasks, has been recently questioned by Poletti and Bonuccelli (2013), who provided the first empirical evidence of impaired affective ToM in 20 patients with aMCI with the RME task. These divergent results concerning affective ToM in patients with aMCI may be, at least in part, due to the different inclusion criteria adopted for patient selection in these studies. Nonetheless, it is important to underline that two more studies investigating the ToM profile of patients with aMCI converged in ascribing to these deficits in recognizing malicious and intentional acts conducted by misbehaving characters (Yamaguchi et al. 2013) and in comprehending pragmatic phenomena, such as sarcasm and metaphor (Maki et al. 2013), suggesting deficits in mentalizing tasks that require the involvement of both the cognitive and the affective components of ToM.

The studies performed by Yamaguchi et al. (2013) and Maki et al. (2013) are relevant not only because they contribute to shedding light on the impaired ToM profile of patients with aMCI but also because they clearly show, even with what concerns social cognitive functioning, that this neurodegenerative condition is a prodromal stage of AD. In fact, in both of these studies, the performances that were shown by patients with aMCI on the ToM tasks were worse than the performances of the healthy controls but systematically better than the performances that were shown by patients with AD, even those in the early stages.

In the last year, another eight studies investigated the mentalizing profiles of patients with frontotemporal dementia (FTD) or AD, in addition to the two studies on comparing patients with aMCI and AD that were previously discussed. In one study (Laisney et al. 2013), patients with mild to moderate AD were compared with healthy controls in a variety of cognitive (preference judgment and first- and second-order false beliefs) and affective (RME) ToM tasks, and they were found to be impaired in solving all of the tasks. Interestingly, this study was the first to find first-order false belief deficits in subjects with mild to moderate AD. In particular, these authors showed that patients with AD may have problems in tasks with minimal executive demands, such as a preference judgment task in which the ability to judge another person's preferences conveyed by gaze is assessed, and that difficulties in inferring a character's mental state, even in simple first-order false belief stories, increase as the disease progresses.

Three more studies (Le Bouc et al. 2012, Bertoux et al. 2013, Narme et al. 2013a) investigated patients with AD and compared their performances with those of patients with FTD. Although, when taken together, these studies confirm previous observations of milder ToM impairments in subjects with AD than in those with FTD (see Poletti et al. 2012), their most important findings concern the possibility of discriminating between these two different neurodegenerative conditions on the basis

of performances in ToM tasks. In particular, Narme et al. (2013a) showed that a socio-emotional index, which was calculated with a battery of tasks, including affective and ToM tests, can discriminate between patients with AD and patients with frontotemporal lobar degeneration, while Bertoux et al. (2013) reported that a task that included two subtests, i.e., a facial emotion recognition test and a shortened version of the FPR test, is the most sensitive, even compared to the well-known Go/No-Go subtest of the Frontal Assessment Battery (FAB) or with the Iowa Gambling Task, in detecting ventromedial prefrontal cortex (VMPFC) dysfunction and, thus, in differentiating AD from behavioural variant FTD (bv-FTD), which is characterized by early and substantial VMPFC dysfunction. Finally, Le Bouc et al. (2012) performed a neuropsychological and neuroimaging study with a non-verbal, three-option false belief task in order to investigate differential impairments in mentalizing in subjects with AD and bv-FTD. These authors found that distinct ToM deficits can distinguish patients with AD from patients with bv-FTD. In fact, in solving this false belief task, patients with AD have a predominant deficit in inferring someone else's belief (a deficit that correlates with low brain metabolism within the left temporo-parietal junction), whereas patients with bv-FTD have selective impairments in inhibiting their own mental perspective (a deficit that correlates with low brain metabolism within the right medial frontal gyrus).

Until now, the strongest evidence that performance on a ToM task may serve as a risk marker for the development of future prefrontal dysfunction and bv-FTD has been provided by Pardini et al. (2013). In a longitudinal study involving 4,150 healthy participants who were aged between 50 and 60 years, these authors administered the RME and a neuropsychological battery. From this extended sample, 83 participants with RME scores that were lower than 2 standard deviations but with otherwise normal neuropsychological evaluations, were selected and evaluated after 2 years, together with a control group of 168 participants with normal RME scores and neuropsychological evaluations. At the follow up compared to baseline, participants in the low-RME group presented a significant reduction in a number of neuropsychological tests, such as the FAB, the Trail Making (B-A score), the phonemic verbal fluency and the Neuropsychiatric Inventory. In contrast, in the control group, there were no significant changes in neuropsychological performances at the follow up compared to baseline. Furthermore, and more strikingly, at follow-up, 12 participants in the low-RME score group and none in the control group presented with neuropsychological, behavioural, and neuroimaging data that were compatible with probable bv-FTD.

Although the potential use of the RME score as a risk marker for the development of FTD needs further confirmation, it is interesting to observe that, in the last year, two studies used this task and found that its score correlates with negative symptoms, such as apathy and indifference, in patients with bv-FTD (Poletti et al. 2013a) and that the low performances on this task shown by patients with bv-FTD at the early stages, as well as the low performances on executive tests, such as the Wisconsin Card Sorting Test and verbal fluency, cannot be explained by a reduction in general intelligence (Roca et al. 2013).

Together with the findings of a recent study showing, with an original perspective, mentalizing deficits in patients with bv-FTD even in the attribution of affective mental states to musical stimuli (Downey et al. 2013), the findings reviewed here further support the need, which

has also been recently stressed by different authors (e.g., Adenzato et al. 2010, Cavallo et al. 2011, Poletti et al. 2012, Schroeter 2012), for introducing validated ToM tasks in the neuropsychological assessments of patients with neurodegenerative diseases. This need is particularly relevant for patients with aMCI, which is characterized by the risk of developing AD, and for the early detection of possible risks of developing bv-FTD degeneration.

4. Theory of Mind in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by motor disturbances (bradykinesia, resting tremor, rigidity, and postural instability), asymmetrical motor onset, and good response to levodopa (Litvan et al. 2003). It is also characterized by the formation of Lewy bodies in nigral regions, limbic and brainstem nuclei, and neocortical regions (Kalaitzakis and Pearce 2009). The loss of dopaminergic neurons in the substantia nigra and the consequent hypostimulation of the prefrontal cortex (in its dorsolateral portion at early PD stages and involving more medial portions in the advanced stages) is associated with the early cognitive dysfunctions, including changes in mood and behaviour (e.g., Aarsland et al. 2009), of patients with PD (Caballol et al. 2007).

In their review, Poletti et al. (2012) concluded that patients with PD may have impairments in tasks of cognitive ToM already from the early stages of the disease, while empirical evidence were less robust and homogeneous for what concerns affective ToM. Three new studies have helped to clarify that the affective component of the ToM may also be impaired in the early/moderate clinical stages. In fact, Poletti and colleagues (2013b) found affective ToM impairments in a sample of 20 patients who had early PD (mean Hoehn and Yahr stage, 1.68) with 5 years of mean disease duration and were assessed by the RME. Further, Narme and colleagues (2013b) reported both second-order cognitive and affective ToM impairments in 23 PD patients who had 6 years of mean disease duration and were assessed by the Yoni task, a task in which both first- and second-order items of affective and cognitive ToM are included (Kalbe et al. 2010, Shamay-Tsoory and Aharon-Peretz 2007). Furthermore, in a study that aimed to investigate the role of fluid intelligence in different frontal deficits that are associated with PD, Roca et al. (2012) found impaired performances on both the RME and the FPR tasks in 32 patients with only 1.47 years of mean disease duration and a Hoehn and Yahr stage of 1.46. In summary, these recent studies have shown that both the cognitive and affective components of ToM may be impaired already from the early stages of the disease.

Another crucial question about ToM abilities in PD is the relationship between these abilities and executive functioning in patients with PD. Even in this case, three recent studies (Anderson et al. 2013, Eddy et al. 2013, Costa et al. 2013) have shed new light on the question. Previous works reported divergent results on the nature of this relationship, with some authors showing a significant association between these two domains and others failing to find such an association (see Poletti et al. 2011). In order to clarify this question, Costa and colleagues (2013) recruited 15 individuals having PD without dementia and who presented with an executive domain deficit and 15 PD patients without cognitive impairments. Using the FPR paradigm, these authors

found a reduced ability to perform ToM tasks in patients with PD having deficits in the dysexecutive spectrum only, while executively unimpaired PD patients performed as accurately as healthy controls. Anderson and colleagues (2013) reported similar conclusions. These authors explored social problem solving in non-demented individuals with PD and assessed the relationships between any observed deficits and overall cognitive and executive function and social cognition. To this aim, a set of tests were administered, including the mentalistic interpretation task for assessing the subjects' abilities to interpret sarcastic remarks or human actions and the social problem tasks for assessing their abilities to generate appropriate solutions to awkward problem situations. Participants were subdivided into a group of 19 PD patients with mild cognitive impairment and a group of 27 PD patients with no evidence of cognitive impairments. Compared to healthy age-matched controls, PD patients without cognitive impairments did not show any evidence of deficits in social cognition or social problem solving. As suggested by Anderson et al. (2013), these findings support the notion that the core pathophysiology of PD itself is not responsible for difficulties in social problem solving nor does the disorder have an inherently detrimental effect on the patients' abilities to understand the actions of others or elements of social communication, such as sarcasm. Finally, results that were in line with this, but less straightforward, were reported by Eddy and colleagues (2013) who explored whether the difficulties in verbal ToM tasks exhibited by individuals with PD could be explained by deficits in executive dysfunction. Using a first-order false belief task and the FPR task, these authors found in three different experiments, an impaired performance of patients with PD on the former task but a preserved performance on the latter. Considering that the FPR task is passed by older children than a first-order false belief task and that it involves second-order ToM, this result was rather surprising. The authors ascribed this unexpected result to a series of possible motivations concerning the different nature of the tasks that were used in their experiments, including the hypothesis that patients with FPR may use intact knowledge about social norms to answer the questions correctly. However, the point relevant to this review is that their study showed that when manipulating the working memory demands in the false belief task by reducing the incidental executive demands associated with this ToM task, it is possible to reduce the number of errors made by patients with PD, providing evidence that executive function can contribute to ToM errors in these patients.

Taken together, the results of the last three reviewed studies converge in showing that PD is not necessarily associated with ToM impairments *per se* and that ToM deficits may occur in patients with PD as a function of the degree of their executive impairment.

5. Theory of Mind in Huntington's Disease

Huntington's disease (HD) is an autosomal dominant-inherited neurodegenerative disorder that is caused by an extended trinucleotide repeat in the *huntingtin* gene on chromosome 4 (Ross and Tabrizi 2011). Individuals at risk can be identified before clinical onset by predictive genetic testing. Patients typically experience uncontrollable choreic movements, which are thought to reflect a dramatic loss of medium spiny neurons in the neo-striatum (Albin et al. 1989). Because of the strong connections between the basal ganglia

and cortical areas, cognitive and neuropsychiatric symptoms are commonly reported in HD, and these include executive dysfunction, depression, breakdown of social relationships, lack of empathy and psychosis (Walker 2007, Rickards et al. 2011). In HD, mild cognitive deficits may be detected in the early clinical stages, but a clear dementia usually appears after several years (Peavy et al. 2010).

Based on the three studies that were available until then, Poletti et al. (2012) concluded that patients with HD may present difficulties in ToM abilities, but that further studies are needed before any conclusions can be made. Two recent studies have contributed to a deeper comprehension of the ToM profiles in patients with HD (Eddy et al. 2012) and pre-manifest HD gene mutation carriers (Saft et al. 2013).

In the study by Eddy and colleagues (2012), the RME and FPR tasks were administered to 16 patients with HD, and sets of neuropsychological tests were used to assess the relationships between executive function and ToM. The authors found that patients with HD demonstrate difficulties on the ToM tasks, including both the cognitive and affective components. Interestingly, the differences in the error rates between patients and healthy controls on the RME were rather striking, and the deficits were consistent across the patient group, suggesting that this task may be particularly sensitive to ToM impairments in patients with HD. For the relationships between ToM performance and executive functioning, patients with HD exhibited significant deficits in executive function, but there was only a significant correlation between higher scores on the verbal fluency task and fewer errors on the RME.

If the study by Eddy et al. (2012) confirms that ToM deficits may be present in the clinical manifestation of HD, the study by Saft and colleagues (2013) contributes to clarifying that these deficits are not necessarily part of the pre-manifest stage. In fact, the authors used a functional brain imaging paradigm and a mentalizing task consisting of six different cartoon stories concerning aspects of cognitive ToM in 30 pre-manifest mutation carriers (pre-HD) and found that pre-HD individuals activate the same mentalizing neural network as a group of healthy controls.

Although these results need to be confirmed by further studies that also include tasks that assess the affective component of ToM, it contributes to our comprehension of the different profiles that characterize the ToM functioning of people with the pre- and post-manifestations of the HD gene mutation.

6. Theory of Mind in Other Neurodegenerative Diseases

The increasing interest in studying the ToM profile of patients with neurodegenerative diseases is attested by the broadening of this interest in the last year to further neurodegenerative diseases that have not been previously analysed, such as essential tremor (ET), and to those that have previously been evaluated only marginally, such as progressive supra-nuclear palsy (PSP).

PSP is a motor disorder with characteristic subcortical pathology that results in a frontal-subcortical disconnection syndrome. In addition to neurological deficits, patients with PSP often present with a frontal dysexecutive disorder with behavioural and personality symptoms, such as social disinhibition and apathy, which is similar to bv-FTD patients. Although ToM

abilities were previously analysed in patients with PSP by Shany-Ur et al. (2012) in an interesting study on the comprehension of insincere communication, a recent study by Ghosh et al. (2012) was the first to incontrovertibly show specific ToM deficits in patients with PSP and to explore the neural correlates of these deficits using voxel-based morphometry (for details of this methodology, see Cicerale et al. 2013). In particular, these authors tested ToM by means of short videos of communicative exchanges in which actors exhibit sincerity, sarcasm or paradoxical sarcasm (i.e., a kind of sarcasm in which the words do not make sense unless the observer is aware that the actor is being sarcastic). Patients with PSP do not have difficulties in interpreting sincere statements (i.e., statements in which the literal and the intended meaning correspond, see Adenzato and Bucciarelli 2008) but find the sarcastic statements difficult, particularly the paradoxical sarcasm. Interestingly, although executive function was impaired in these patients, ToM performance was still impaired when the Brixton test, which is an untimed test of executive function with minimal motor demands, was included as a covariate. Finally, these authors showed that ToM performance correlates negatively with grey matter atrophy in the anterior rostral medial frontal cortex as well as in the right superior temporal gyrus and left temporo-parietal junction, which are all brain areas crucial for the comprehension of communicative intentions (Walter et al. 2004, Ciaramidaro et al. 2007, Enrici et al. 2011).

ET has been classically considered a clinical syndrome of action tremor in the upper limbs in the absence of other neurologic signs, even if non-motor symptoms, such as reduced verbal fluency and deficits of mental set-shifting and working memory, have been described (e.g., Kim et al. 2009, Passamonti et al. 2011). Recently, Santangelo et al. (2013) investigated for the first time both the cognitive and the affective ToM profiles of these patients. To this aim, these authors administered to 30 patients with ET a cognitive ToM task consisting of 13 written stories in which two or more characters interacted with each other and an affective ToM task consisting of 35 written stories describing emotional situations. The participants in both tasks had to read each story and then comprehend someone else's mental state. After co-varying for amnesic, behavioural, and quality of life scores, the main finding of the study was a dissociation between the cognitive and affective ToM, that is, patients with ET show selective impairment in cognitive ToM, which is significantly associated with frontal tasks, such as the FAB, WCST, and phonological fluency, in the presence of a preserved affective ToM. Santangelo et al. (2013) tentatively related this impairment to dysfunctions of prefrontal-cerebellum circuitry.

7. Conclusions

There is fast-growing interest in the study of ToM abilities in neurodegenerative diseases. The research in this field is highly promising, although some limitations are still present. Apart from the well-known problems concerning the differences among the populations and tasks used in the studies, too little effort has been, until now, dedicated to perform longitudinal studies. The lack of such studies is rather surprising considering the developmental nature of any neurodegenerative disease. Thus, it is not by chance that one of the most interesting result has been provided by Pardini et al. (2013) in the longitudinal study previously reviewed

showing the potential of the RME score as a risk marker for the development of FTD.

In neurodegenerative diseases, for the relationship between cognitive impairments, especially in the dysexecutive spectrum, and ToM deficits, new modalities are necessary, in addition to the standard correlations between the patients' score and the executive and ToM tasks. We suggest that an effort should be made in investigating the effects of cognitive training on ToM abilities in order to better comprehend if executive functions and ToM are functionally independent by following the approach still pursued for neuropsychiatric conditions, such as autism and schizophrenia (e.g., Fisher and Happé 2005, Subramaniam et al. 2012, Cavallo et al. 2013).

In spite of these limitations, the data discussed here strongly suggest overall that a neuropsychological assessment of patients with neurodegenerative diseases should routinely include an accurate investigation of ToM abilities. Increasing evidence (e.g., Torralva et al. 2009, Funkiewiez et al. 2012, Le Bouc et al. 2012, Bertoux et al. 2013, Narme et al. 2013a, Pardini et al. 2013) has shown that different ToM tasks may help clinicians in the diagnostic process and caregivers in understanding the behavioural problems that are often shown by their suffering relatives.

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