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Running title: ToM in neurodegenerative diseases

**Cognitive and affective Theory of Mind in neurodegenerative diseases:
Neuropsychological, neuroanatomical and neurochemical levels**

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Abstract

The paper reviews of all of the current evidence on Theory of Mind (ToM) abilities in patients with neurodegenerative diseases. ToM refers to the abilities to attribute mental states to others. Two neural systems are involved in processing other people's beliefs and intentions (cognitive component) and others' emotions and feelings (affective component). We hypothesize that patients with different neurodegenerative diseases may present different patterns of ToM deficits on the basis of how different neuropathological processes affect the neural bases of ToM components during the progression of a disease. The studies we reviewed provided evidence of a deficit of the cognitive ToM component in cortical (Alzheimer's disease and frontotemporal dementia) and frontal-subcortical (amyotrophic lateral sclerosis and basal ganglia disorders) neurodegenerative diseases. As regards the affective ToM component, it resulted markedly impaired in frontotemporal dementia; it also resulted that performances in tasks assessing this process are heterogeneous in Parkinson's disease and amyotrophic lateral sclerosis. The findings presented support the opportunity to introduce validated ToM tasks in the neuropsychological assessment of neurodegenerative diseases.

Keywords: Alzheimer's disease, Amyotrophic lateral sclerosis, Basal ganglia disorders, Executive functions, Frontotemporal dementia, Huntington's disease, Neurodegenerative diseases, Parkinson's disease, Prefrontal cortex, Semantic dementia, Theory of Mind.

1. Introduction

The term Theory of Mind (ToM) refers to the abilities to attribute mental states to others and to predict, describe, and explain behaviour on the basis of such mental states (Baron-Cohen 1995; Premack and Woodruff, 1978). Usually assessed in subjects with various psychiatric disorders such as schizophrenia (e.g. Walter et al., 2009), autism (e.g. Baron-Cohen, 1995), anorexia nervosa (e.g. Russell et al., 2009), depression (e.g. Wang et al., 2008), and borderline personality disorder (e.g. Arntz et al., 2009), in recent years researchers have also started to assess ToM abilities in patients with neurodegenerative diseases, such as Alzheimer's disease, frontotemporal dementia, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Investigating if and how ToM is impaired when a neuropathology progressively involves cortical and subcortical brain structures, these studies have the aim to better understand the neuropsychological, neuroanatomical, and neurochemical bases of ToM.

The present paper provides a review of all of the current evidence on ToM abilities in patients with neurodegenerative diseases. The studies included were identified through searches in the ISI Web of knowledge, Medline, and PsychInfo electronic databases; only studies in the English language were included. The final search for this review was carried out in February 2012. The keywords used for the search were 'Alzheimer's disease', 'Frontotemporal Dementia', 'Parkinson's disease', 'Huntington's disease', 'Amyotrophic Lateral Sclerosis', 'Dementia', and 'Neurodegenerative disease' combined with each of the following terms: 'Mentalizing', 'Mindreading', and 'Theory of Mind'. Only studies that reported data on performance in ToM tasks by patients diagnosed according to accepted consensus guidelines for clinical or pathological diagnosis were included.

2. The neural bases of the Theory of Mind

The ability to recognize, manipulate, and behave with respect to socially relevant information requires neural systems that process perception of social signals and connect such perception to motivation, emotion, and adaptive behaviour (Adolphs, 2009; Lieberman, 2007; Tamietto and de Gelder, 2008). Findings from a decade of neuroimaging studies have shown the existence of a distributed neural network underlying the abilities to understand and to predict other people's behaviour by attributing independent mental states to them, i.e. ToM abilities. This network includes, at least, the complex formed by the posterior superior temporal sulci (pSTS) and by the adjacent temporo-parietal junctions (TPJ) areas, the precuneus, and the prefrontal cortex (PFC) (especially its medial portions) (Carrington and Bailey, 2009; Ciaramidaro et al., 2007; Enrici et al., 2011; Van Overwalle and Baetens, 2009; Walter et al., 2004). Furthermore, findings from lesion studies have highlighted the key role of the prefrontal and frontal brain areas in ToM abilities (Channon and Crawford, 2000; Lee et al., 2010; Roca et al., 2011; Rowe et al., 2001; Stone et al., 1998; Stuss et al., 2001).

Although ToM is a topic that has increasingly attracted interest in cognitive neuroscience during the last years, research has only recently begun to examine the subcomponents of the complex abilities we refer to as ToM. A recent topic in the field is to distinguish the different roles of ToM neural underpinnings, at least for what concerns the PFC. Shamay-Tsoory and colleagues (2009; 2010) proposed a model where two separate systems are involved in processing inferences about others' beliefs and intentions (cognitive ToM) and inferences about other people's emotions and feelings (affective ToM). Indeed, different lesion studies have provided evidence that ToM could be considered a multidimensional construct and that different ToM subcomponents are differently recruited by cognitive and affective ToM tasks such as the false-beliefs tasks and the Reading the Mind in the Eyes task, respectively (see Figure 1 for the neural systems underlying cognitive and

affective ToM subcomponents and section 3 for a detailed description of the ToM tasks).

Figure 1 about here

Shamay-Tsoory and colleagues (2005; 2006) firstly showed that, in adult subjects, performances in affective ToM tasks are impaired when the ventromedial PFC is damaged and not when the lesion affects other areas of the PFC. Thus, the ventromedial PFC is supposed to play a unique role in affective ToM reasoning rather than a general role in ToM. Recent evidence comes also from a study in which patients with bilateral ventromedial PFC lesions did not show deficits in complex forms of cognitive ToM tasks involving the use of common ground knowledge in a social interaction (Gupta et al., 2012). Furthermore, the only neuroimaging study that has compared the neural correlates of cognitive vs. affective ToM tasks reported greater ventromedial PFC activation during affective ToM than during cognitive ToM (Sebastian et al., 2012).

While the role of the ventromedial PFC for affective ToM is well-documented, the neural substrates of cognitive ToM are less well-defined. Nevertheless, Kalbe et al. (2010) provided evidence of an important role of the dorsolateral PFC in cognitive ToM tasks showing that a repetitive transcranial magnetic stimulation over this area has a selective effect on cognitive but not on affective ToM tasks. An important contribution of the different roles of the ventromedial and dorsolateral PFC in ToM was recently provided by Xi et al. (2011). These authors used a complex form of ToM task including both affective and cognitive subcomponents, i.e. the Faux Pas Recognition test (FPR) (see below). The findings of this study show that patients with ventromedial and dorsolateral PFC lesions have impaired ability

on FPR, but they were impaired on different aspects of this test. In particular, while patients with ventromedial PFC lesions made errors in detecting the presence of a faux pas (the affective component of the test), patients with dorsolateral PFC lesions recognized the occurrence of a faux pas but did not correctly make inferences about the mental state of others (the cognitive component of the test).

Finally, recent findings suggest that while the dorsolateral and the ventromedial PFCs exhibit preferences for the processing of cognitive or affective mental states, the posterior regions of the ToM network (i.e. the precuneus, TPJ, and pSTS) do not exhibit this preference but play a major role in assigning agency to these mental states (Abu-Akel and Shamay-Tsoory, 2011).

3. Theory of Mind experimental tasks

The distinction between affective and cognitive subcomponents of ToM was essentially demonstrated by using different ToM tests with respect to their cognitive (e.g. belief about belief) or affective (e.g. belief about feelings) request. Several tests have been developed to assess affective and cognitive ToM subcomponents in adults. As these tests are the same used in populations with neurodegenerative diseases, now we briefly describe the most commonly used ToM tests and the kinds of experimental tasks that participants are invited to complete.

The first-order false-belief and the second-order false-belief tests are considered the prototypical tasks for the assessment of cognitive ToM; the first-order false-belief test assesses an individual's ability to infer that someone has a (mistaken) belief about the world (e.g. A's beliefs about the location of an object) that is different from the individual's own (true) belief (Baron-Cohen et al., 1985; Wimmer and Perner, 1983). The second-order false-belief test (Baron-Cohen, 1989; Perner and Wimmer, 1985) is more complex than the first-order version since in this situation it is not sufficient to infer another person's thoughts about

the world, but it is crucial to form beliefs about the content of that person's mind (e.g. B's beliefs about A's beliefs about the location of an object).

Reading the Mind in the Eyes (RME) is considered the prototypical task for the assessment of affective ToM. The RME is an advanced test consisting of the presentation of photographs of the eye regions of human faces (Baron-Cohen et al., 1997; 2001). Participants are required to choose which word best describes what the individual in the photograph is thinking or feeling.

The Faux Pas Recognition (FPR) test permits to assess both the cognitive and the affective components of ToM. In the FPR test, the participant hears 10 stories read aloud, containing a social faux pas and 10 control stories reporting a minor conflict but in which no faux pas is committed (Stone et al., 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 (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 involved in the stories (the cognitive component).

In the Yoni task (Kalbe et al., 2010; Shamay-Tsoory and Aharon-Peretz, 2007), a face named 'Yoni' is shown, in the middle of a computer screen, with four coloured pictures in the corners showing either faces and/or examples of a semantic category (e.g. animals, fruits). Participants have to evaluate which of these four pictures best corresponds to a sentence contemporaneously presented on each screen about which image Yoni is referencing. The items can be subdivided into three types of categories that correspond to affective ToM, cognitive ToM, and control conditions. While the answers for the control condition only require an analysis of the character's physical attributes, the choices in the affective and cognitive ToM items imply mentalizing based on verbal cues contained in the sentence, eye gaze, and/or facial expression (e.g. cognitive component: Yoni is thinking of..., affective

component: Yoni loves..., and control condition: Yoni is close to...). Items differ in complexity with both first- and second-order items included.

In the Strange Stories task (Happé, 1994) participants read short vignettes and are asked to explain why a character says something that is not literally true. Successful performance requires attribution of mental states such as desires, beliefs or intentions, and also higher order mental states such as one character's belief about what another character knows. There are no specific considerations concerning the role of this task in affective rather than in cognitive ToM, although it could be considered mainly a cognitive ToM task.

In recent years, the ToM tasks described here were used in a series of studies involving patients with different neurodegenerative pathologies. The power of cognitive neuroscience comes from using convergent tools to investigate the same theoretical question and to reveal the anatomy and time-course of a given brain function (Adenzato and Garbarini, 2006; Price et al., 1999; Rorden and Karnath, 2004). Considering that ToM can be distinguished at least in two subcomponents (affective and cognitive) with different neural bases, neurodegenerative pathologies offer a crucial contribution to the study of this function. We hypothesize that patients with different neurodegenerative diseases may present different patterns of ToM deficits on the basis of how different neuropathological processes affect the neural bases of ToM components during the progression of the disease. Accordingly, patients at diverse stages of the disease should present with different patterns of ToM dysfunction.

4. Neuropathological changes

4.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia among older people. In the early stages of AD, neurodegeneration occurs in the medial temporal lobes, including the hippocampus and the entorhinal cortex. As the disease progresses, other cortical areas, such as

the lateral, temporal, frontal, and parietal cortices, are typically affected (Braak and Braak, 1991; Naggara et al., 2006). The neurodegeneration in the basal forebrain leads to a decrease in acetylcholine levels throughout the brain (Schliebs, 2005) that together with atrophy of the aforementioned brain structures results in a progressive decline of memory functions as well as language and visuospatial abilities (Hodges, 2006). Other cognitive domains, such as executive functions, might also be affected (Amieva et al., 2004; Huntley and Howard, 2010).

4.2. Frontotemporal dementia and amyotrophic lateral sclerosis

Frontotemporal Dementia (FTD) is the second-most common young-onset dementia and is clinically characterized by progressive behavioural alteration, executive dysfunction, and language difficulties, due to pathological changes occurring within the anterior temporal and PFC (Neary et al., 1998). FTD exists in three variants characterized by three prototypical neurobehavioural syndromes and associated with characteristic patterns of cerebral atrophy (Schroeter et al., 2007): behavioural variant FTD (bvFTD), semantic dementia, and progressive non-fluent aphasia. Patients with semantic dementia and with progressive non-fluent aphasia are mainly characterized at early stages by language deficits related to alterations in the inferior and middle temporal gyri (Galton et al., 2001) and in the left frontal and anterior temporal brain regions (Gorno-Tempini et al., 2011), respectively. BvFTD patients are characterized at early stages by profound alterations in personality and social conduct, apathy, disinhibition, and lack of insight (Adenzato et al., 2010; Piguet et al., 2011) related to early alterations in the ventromedial regions of the PFC (Hornberger et al., 2011; Peters et al., 2006); with the progression of the disease, these alterations involve also more posterior cortical areas (Diehl-Schmid et al., 2007).

During the past decade there has been increasing awareness of the overlap between the FTD spectrum and extrapyramidal diseases, such as parkinsonism (corticobasal degeneration

and progressive supranuclear palsy: Lee et al., 2011; Ludolph et al., 2009) and motor neuron disease - especially amyotrophic lateral sclerosis (ALS) (Lomen-Hoerth et al., 2002). In particular, a link has been established between FTD and ALS on neuropathological (Lipton et al., 2004), neuroimaging (Jeong et al., 2005), and cognitive (Ringholz et al., 2005) grounds. Structural and functional neuroimaging have demonstrated that ALS is associated with abnormalities localized mainly in the frontal lobes (Abrahams et al., 1996; Kato et al., 1993), and neuropathological investigations have shown the pathological involvement of PFC (Maekawa et al., 2004). The frontal syndrome that appears to characterize up to 50% of ALS has been noted to be similar to the profile that characterizes patients with FTD, and it has been proposed that ALS may represent a point on a clinical continuum ranging from ALS, ALS/FTD, through to FTD (Bigio et al., 2003).

4.3. Parkinson's disease and Huntington's disease

In contrast to AD and diseases of the FTD spectrum, which are predominantly characterized by degeneration in cortical brain areas, Parkinson's disease (PD) and Huntington's disease (HD) are characterized in the early clinical stages by neurodegeneration of the subcortical structures. For example, progressive loss of dopaminergic neurons in the substantia nigra, which is an essential component of the basal ganglia circuitry, is a characteristic feature of PD (Kish et al., 1988). Loss of these dopaminergic neurons is considered to be one of the underlying mechanisms that contribute to motor symptoms such as bradykinesia, rigidity, and tremor (Jankovic, 2008). The dopamine striatal depletion and the consequent hypostimulation of the PFC (in its dorsolateral portion at early PD stages, also involving more medial portions, in the advanced stages) are also considered the underlying mechanisms of the early executive deficits of PD patients (Aarsland et al., 2010). With the progression of PD, the cortical

diffusion of Lewy bodies (Braak et al., 2003; Scatton et al., 1982) often results in the development of dementia (Emre et al., 2007).

In contrast, patients with HD 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). Also, in HD patients, as in PD, considering the strong connections between the basal ganglia and the cortical areas, cognitive and neuropsychiatric symptoms are commonly reported, including executive dysfunction, depression, and psychosis (Rickards et al., 2011).

The neurodegenerative diseases described have different aetiologies and present different neuropathological changes, neurochemical alterations, neuropsychological patterns, and clinical courses. From the neuroanatomical point of view, the neuropathology in AD and in the FTD clinical syndromes involves cortical territories since the early clinical stages (Braak and Braak, 1991; Naggara et al., 2006; Seelaar et al., 2011), while the neuropathology in PD and HD involves basal ganglia in the early clinical stages, and the cortical territories are involved in more advanced stages of the disease (Braak et al., 2003). Also, from the neuropsychological point of view, these diseases present very different patterns, i.e. when AD is diagnosed, patients present a clear dementia, involving at least three cognitive domains, such as memory, language, and visuospatial functions (Hodges, 2006); otherwise, the diagnosis of bvFTD is mainly based on behavioural alterations, and in early clinical stages patients may appear cognitively preserved although clear or subtle deficits may involve orbitofrontal/ventromedial functions, such as decision-making (Gleichgerricht et al., 2010; Wittenberg et al., 2008). In PD, as well as in HD, mild cognitive deficits may be detected since the early clinical stages (Aarsland et al., 2009) but a clear dementia usually appears after several years (Emre et al., 2007; Peavy et al., 2010). Finally, ALS has traditionally been

considered a neurodegenerative condition affecting exclusively the motor system, with no repercussions on the cognitive domain. However, numerous studies have now challenged this view, demonstrating the presence of significant cognitive impairment predominantly in the realm of executive functions in a significant proportion of ALS patients and in language functions in some patients (Abrahams et al., 2005; Lomen-Hoerth et al., 2003).

Researches in the realm of social cognition shed a new light on how the neurodegenerative diseases described here present deficits in various ToM tasks. Considering at least the neuropathological and neuropsychological differences between the neurodegenerative diseases, we now test the hypothesis that the findings of studies on ToM abilities in these diseases describe ToM deficits on the basis of how different neuropathological processes during the progression of the diseases affect differently (a) the anterior and posterior regions of the ToM network, (b) the frontal and prefrontal regions, and (c) the cortical and subcortical brain areas.

5. Neurodegenerative diseases and Theory of Mind

Tables 1 and 2 describe and summarize the main findings of the studies that have assessed ToM abilities in patients with neurodegenerative diseases.

5.1. Alzheimer's disease

From the search in electronic databases, we found 10 group studies that assessed ToM in patients with AD (see Table 1). In the first study (Cuerva et al., 2001), AD patients resulted impaired in the second-order false-belief tasks. Subsequent studies (Fernandez-Duque et al., 2009; Gregory et al., 2002; Youmans and Bourgeois, 2010; Zaitchik et al., 2006) found similar results, i.e. AD patients performed correctly the low-cognitive demanding ToM tasks but had worse performances than the healthy controls in the second-order false-belief tasks.

Interestingly, another study (Verdon et al., 2007), adopting a ToM cartoon task, usually adopted in fMRI studies (Brunet et al., 2000), found a specific impairment in AD patients in the understanding of psychological causes of events, with a spared understanding of physical causes.

In a recent study, Castelli and colleagues (2011) found that performances of AD patients in verbal ToM tasks correlated with cognitive measures of executive functions and verbal episodic memory, and performances in the ToM tasks supported by cartoons correlated with cognitive measures of visuospatial abilities. Finally, another recent study (Shany-Ur et al., 2011) assessed a group of patients at an early stage of AD; authors focused on the ability to detect insincere communications, using the Social Inference test (McDonald et al., 2003), together with first- and second-order false-belief tasks. In comparison to healthy controls, AD patients had preserved performances in the Social Inference test, but an impaired performance in both the false-belief tasks.

Globally considered, these studies clearly showed that AD patients present an impairment in tasks that assess the cognitive component of ToM and have a demanding cognitive load, such as second-order false-belief tasks (Castelli et al., 2011; Cuerva et al., 2001; Fernandez-Duque et al., 2009; Gregory et al., 2002; Shany-Ur et al., 2011; Zaitchik et al., 2004; 2006). Indeed, almost all the studies reported better performances in the tasks of cognitive ToM with a low-demanding cognitive load, as the first-order false-belief tasks. More controversial are the results on tasks that assessed the affective ToM component in AD, adopted in only three studies: one study reported preserved performances in the RME and in the FPR (Gregory et al., 2002), one study reported a preserved FPR performance of a sample including 11 AD patients and 11 patients with amnesic mild cognitive impairment (Funkiewiez et al., 2012), and one study reported a preserved performance in an emotion-situation understanding task but with an impaired performance in the RME (Castelli et al.,

2011). This suggests that to date no conclusions can be made on affective ToM in AD and further studies are needed on this topic.

5.2. Frontotemporal dementia and amyotrophic lateral sclerosis

From the search in electronic databases, we found 3 case studies and 10 group studies that assessed ToM abilities in patients with bvFTD (one of them also assessed ToM abilities in patients with progressive non-fluent aphasia or semantic dementia mixing them in a single group), one study that specifically assessed ToM abilities in patients with semantic dementia, and four studies on patients with ALS (see Table 1).

5.2.1. Behavioural variant of frontotemporal dementia

The first investigations of ToM abilities in bvFTD patients were described in two case-reports. Lough et al. (2001) examined the case of a 47-year-old man with a bvFTD diagnosis and exhibiting severe antisocial behaviour. Although a general neuropsychological assessment showed limited cognitive impairment, a ToM battery revealed that the patient failed both the first- and second-order ToM tests and was unable to recognize a single faux pas although he correctly answered the control questions. His ability to detect emotional states (measured via the RME test) was intact. Similar results were found by Lough and Hodges (2002) in a further single case study, i.e. the patient was administered the previously described ToM tasks, and, interestingly, he showed severely impaired performances on all of them with a clear dissociation between executive functions and ToM abilities. A more recent case study (Poletti et al., 2011a) investigated affective ToM ability with the RME in a case of a phenocopy syndrome of bvFTD (presence of behavioural alterations and absence of cortical atrophy and hypometabolism: Kipps et al., 2010), which was characterized by pathological lying, detecting a severe impairment in this task.

With the only exception of the study by Fernandez-Duque et al. (2009) that found a preserved performance in the first-order false-belief task, all of the group studies on bvFTD patients found a common severe deficit involving both the cognitive component and the affective component of ToM (Eslinger et al., 2007; Funkiewiez et al., 2012; Gleichgerrcht et al., 2011; Gregory et al., 2002; Lough et al., 2006; Snowden et al., 2003; Torralva et al., 2007; 2009). 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 bvFTD and HD. To this aim, the authors used single cartoon, cartoon pairs, story comprehension (Happé et al., 1999), and judgment of preference task (Baron-Cohen et al., 1995). Compared to healthy controls, the performance of bvFTD patients was severely impaired on all of the ToM tasks. The authors paid particular attention to bvFTD patients' performance on the judgment of preference task, a task very similar to the Yoni task. Interestingly, bvFTD patients failed to ascribe preference ('Which one does he like?') but had no difficulty in reporting the direction of eye gaze ('Which one is he looking at?'). As these two sub-tasks differed in terms of mental state attribution but not in terms of the cognitive load required, the authors suggested that the performance differences shown by the bvFTD patients provided evidence for a specific ToM impairment.

Eslinger et al. (2007) were interested in studying the ability to solve standardized social dilemmas in patients with FTD. They were divided into two subgroups: patients with social and executive impairments (SOC/EXEC, i.e. the bvFTD) and patients with 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 and Guilford, 1965) requiring participants to identify the thoughts, feelings, and intentions of the 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 et al., 1998) and asked participants to answer questions requiring the attribution of mental states to the characters. Interestingly, impaired social judgments in bvFTD patients were associated with ToM and cognitive flexibility deficits and were related to right hemisphere cortical atrophy, which was localized 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 at a lesser degree than bvFTD patients. Unfortunately, Eslinger et al. (2007) do not report direct comparison between the performance of APH patients and healthy controls.

A recent study (Gleichgerrcht et al., 2011) investigated the relationships between ToM abilities (with the RME and the FPR), decision-making (with the IGT), and moral judgments (Mendez et al., 2005) in bvFTD patients. BvFTD patients were divided on the basis of their response to the footbridge moral dilemma (Thomson and Parent, 1986), in which a trolley was going down the tracks and threatened to kill five people. Each patient was asked to imagine that he/she was standing next to a large stranger on a footbridge that spanned the tracks, between the oncoming trolley and the five people. The patient was instructed that the only way to save five people was to push that stranger off the bridge, onto the tracks below; the stranger would die, but his large body would stop the trolley from killing the five men. Then, the patient was asked whether he/she would push the large man onto the tracks, saving five men but killing him. BvFTD patients that would push the man onto the tracks reported lower scores in the RME but not in the FPR in comparison with bvFTD patients that would not push the man onto the tracks, suggesting that altered dilemmatic judgments may be related to impaired affective ToM. Among all of the studies we reviewed, that of Gleichgerrcht and colleagues (2011) is the only one in which a control group was not included.

Finally, a previously discussed study (Shany-Ur et al., 2011) assessed a group of bvFTD patients focusing on the ability to detect insincere communications, using the Social Inference test and the false-belief tasks. Also controlling for cognitive dysfunction, bvFTD patients showed marked difficulties in all tasks, providing evidence of a diffuse ToM impairment. It is worth noticing that the study by Shany-Ur et al. (2011) is the only one in which ToM abilities were also assessed in patients with progressive supranuclear palsy (PSP). PSP is a motor disorder with characteristic subcortical pathology resulting in a frontal-subcortical disconnection syndrome. In addition to neurological deficits, patients with PSP often present a frontal dysexecutive disorder with behavioural and personality symptoms such as social disinhibition and apathy, similar to bvFTD patients. Shany-Ur et al. (2011) found that PSP patients could understand literal, truthful remarks as well as healthy control could, but performed poorly on ToM tests (though not to the same extent as patients with bvFTD). Interestingly, PSP patients showed a dissociation: though they did not have difficulty representing others' knowledge when the information was explicitly presented visually, they were impaired at representing others' explicitly stated opinions.

Globally considered, studies on bvFTD patients found a common severe deficit involving both the cognitive and the affective component of ToM.

5.2.2. Semantic dementia

A part of the study previously described (Eslinger et al., 2007) in which patients with semantic dementia were mixed with patients with non-fluent progressive aphasia, the only study that analyzed ToM abilities in patients with semantic dementia, is the one recently performed by Duval and colleagues (2012). These authors used two cognitive ToM tasks, i.e. the attribution of intention task (Brunet et al., 2000), a story completion task in comic strip form where subjects have to choose the logical story ending by interpreting the intention of

the characters depicted, and the false-belief tasks (first- and second-order); two affective ToM tasks, i.e. the RME and the ToM's taste, an original task similar to the Yoni task. In addition to the previous 'objective' ToM assessment, they performed a 'subjective' ToM assessment using an original self-rating questionnaire to assess awareness of the putative ToM deficit in both subcomponents: the ToM cognitive awareness (e.g. 'I can easily deduce someone's intentions') and the ToM affective awareness (e.g. 'I can easily identify the emotions that a person is experiencing'). Findings revealed that, compared to healthy controls, patients with semantic dementia showed impairment in both the affective and cognitive dimensions of ToM. One important distinction between the patients' deficits in the two ToM dimensions was the awareness; their results showed the patients impairment of cognitive functioning awareness whereas they were aware of their affective ToM disturbance. The authors suggested that the patients with semantic dementia, at least in the mild stage of the disease, were aware of their affective ToM disturbance but revealed a loss of insight for their cognitive ToM difficulty.

5.2.3. Amyotrophic lateral sclerosis

Four studies have investigated ToM abilities in patients with ALS. Gibbons and colleagues (2007) used cartoons and stories that required participants to attribute mental states to others, as well as some that pertained to physical events. The analysis of individual patient's results revealed a heterogeneous range of performance ranging from normal to severely impaired. Furthermore, the qualitative analysis of the results showed that the errors made by the patients with ALS were similar to the ones made by patients with FTD (Snowden et al., 2003) and that the ToM performance of ALS patients correlated with cognitive measures of executive functioning. An altered social awareness and a difficulty in identifying the presence of a faux pas in social situations were reported by Meier and colleagues (2010). Using the FPR test,

they revealed that 6 of 18 patients with ALS were significantly impaired on the faux pas condition and found a specific effect of the task, i.e. their ALS patients showed poorer performances in stories containing social interactions that involved a faux pas than in the control stories in which the faux pas was removed. Interestingly, ALS patients also failed a decision-making task (the Holiday Apartment Task) assessing the strategic processes involved in multiple-attribute decision-making without ambiguity or risk. More recently, Girardi et al. (2011) described deficits in ALS patients on the IGT and in a separate group of patients in the judgment of preference task. Only some of the patients who were impaired on this latter task also showed evidence of executive dysfunction. Furthermore, these authors showed a trend towards significantly lower RME accuracy scores in ALS patients compared to healthy controls.

The last study that has investigated ToM performance in ALS is the one by Cavallo and colleagues (2011). These authors used the RME task and a story-completion task presented in a comic strip form, similar to the attribution of the intention task previously described (Brunet et al., 2000) that distinguishes between social and non-social contexts. Interestingly, to this latter cognitive task, the performance of patients with ALS and healthy controls significantly differed on the comprehension of social context only, with impairment in patients with ALS. Single-case analysis confirmed the findings at an individual level with 12 of the 15 patients showing worse performances in the comprehension of social context than in the comprehension of non-social context. Regarding the RME task, the ALS patients' performance either as a group or as individuals did not differ from the healthy controls' performances.

Overall, these few studies preliminary showed that ALS patients may have difficulties in ToM abilities, although this conclusion should be taken cautiously since in every study we reviewed within the same group of patients heterogeneous performances emerged, ranging

from normal to slightly or severely impaired. It seems plausible to suggest that this heterogeneity is mainly due to the multisystemic nature of this neurodegenerative disorder.

Table 1 about here

5.3. Basal ganglia disorders

From the search in electronic databases, we found 13 group studies that assessed ToM abilities in patients with PD and 3 studies that assessed ToM abilities in patients with HD (see Table 2).

5.3.1. Parkinson's disease

To define the operative criteria that distinguish the clinical stages of PD, we present the findings of studies on PD patients by adopting the Hoehn and Yahr Staging Scale (H&Y: Hoehn and Yahr, 1967). The modified version of this scale describes the progression of PD in seven stages. Following the suggestions of the Movement Disorder Society Task Force report on the H&Y (Goetz et al., 2004), we defined the clinical stages of PD as early (H&Y Stages 1, 1.5, and 2), moderate (H&Y Stage 2.5 and 3), and advanced (H&Y Stages 4 and 5).

Most of the studies that investigated the cognitive component of ToM, assessed patients at early/moderate PD stages and found an impairment in this ability in different tasks, such as the Strange Stories task (Santangelo et al., 2012), the first-order false-belief tasks (Mengelberg and Siegert, 2003), the second-order false-belief tasks (Monetta et al., 2009; Saltzman et al., 2000), the Cartoon task (Yu et al., 2012), the second-order cognitive component of the Yoni task (Bodden et al., 2010), and the cognitive component of the FPR,

(Kawamura and Koyama, 2007; Roca et al., 2010) although preserved performances of early PD patients in the cognitive component of ToM have been reported (Peron et al., 2009). Indeed, Peron et al., (2009) administered the FPR to two different samples of patients at different stages of PD (early and moderate/advanced). Early PD patients had preserved performances, while more advanced PD patients showed selective difficulties in the cognitive component of the FPR. It is worth noting that only in this study early PD patients were tested both ‘on’ and ‘off’ dopaminergic therapy, reporting no differences between these different conditions. Moreover, in the study of Roca et al. (2010), the FPR task was administered to both early-medicated PD patients and unmedicated de novo PD patients. It is important to note that this study is the only one involving unmedicated PD patients. Healthy controls outperformed the medicated PD patients but not the unmedicated PD patients in the FPR total score. Considering cognitive and affective components of the FPR, healthy controls and PD patients, independently from medication, performed similarly the affective component, while a significant difference was found in the cognitive component; healthy controls outperformed both medicated and unmedicated PD patients and no differences were found between medicated and unmedicated PD patients.

In relation to the affective ToM component, seven studies adopted the RME test in patients with PD. Two studies included only early PD patients (Roca et al., 2010; Tsuruya et al., 2011); four studies included in the same sample, i.e. both early PD patients and moderate PD patients (Bodden et al., 2010; Euteneuer et al., 2009; Mimura et al., 2006; Peron et al., 2009; 2010), and one study distinguished early PD patients and moderate PD patients (Peron et al., 2009). Four of these studies showed that the performance of medicated patients in the RME task may be preserved in the early stages of PD (Peron et al., 2009; 2010; Roca et al., 2010), up to a mean disease duration of 7.1 years (Euteneuer et al., 2009) and 10.2 years (Peron et al., 2009). Instead, three studies reported lower RME performances of medicated

PD patients in comparison to healthy controls (Bodden et al., 2010; Mimura et al., 2006; Tsuruya et al., 2011). In the study by Tsuruya and colleagues (2011), patients had a mean PD duration of 5.1 ± 0.7 years and were in early stages (H&Y Mean Stage 1.5 ± 0.7), while in the study by Bodden and colleagues (2010), patients had a mean PD duration of 5.1 ± 2.8 years but the clinical staging of PD was heterogeneous, with both early PD and moderate PD patients (H&Y Mean Stage 2.5, Range 1–3). In another study (Mimura et al., 2006), medicated patients at early PD stages and at moderate PD stages (Range of H&Y Stage 1–3) obtained poorer scores than healthy controls, but authors highlighted that RME performances by both PD patients and healthy controls were relatively high. Summarizing, the majority of studies reported that PD patients may have preserved RME performances, even after ten years of disease and that mild difficulties may emerge at least after five years of PD.

Four studies adopted the FPR in PD patients, converging on preserved performances of PD patients in the affective component of the task (Kawamura and Koyama, 2007; Peron et al., 2009; Roca et al., 2010; Yu et al., 2011), while only two studies reported an impaired affective ToM component in early PD patients (Bodden et al., 2010; Santangelo et al., 2012), but these studies adopted tasks not adopted in other studies (the Yoni task and the Emotion Attribution task), therefore these findings need further empirical investigation.

Overall, these studies globally showed that PD patients may have impairments in tasks of cognitive ToM. Although less robust and homogeneous in comparison to the cognitive ToM, empirical evidence preliminary suggests that affective ToM may be preserved in the early/moderate clinical stages of PD and mild difficulties may emerge at least after five years of PD; instead, no meaningful conclusions can be made at this time on patients in advanced stages of PD, and this subgroup of PD patients deserves further empirical investigation.

5.3.2. Huntington's disease

Only 3 studies investigated ToM abilities in HD patients. As previously reported, Snowden et al. (2003) investigated the ability to interpret social situations and attribute mental states to others in patients with bvFTD and HD. Compared to healthy controls, the HD group showed milder impairment in interpreting cartoons and stories and normal preference judgments.

Allain et al. (2011) administered a cognitive ToM task (attributions of intentions) and an affective ToM task to early HD patients and healthy controls. HD patients failed both tasks in comparison to controls, and the performance in the cognitive ToM task correlated with the measures of executive functioning. Lastly, Brune et al. (2011) administered six cartoon picture stories and related questionnaires to HD patients, schizophrenic patients, and healthy controls. The clinical groups performed similarly and worse than healthy controls the ToM tasks; ToM performances of HD patients correlated with intelligence quotient and two indices of executive tasks (perseverative errors in a card-sorting test; the Zoo Map Test).

Taken together, these studies preliminary showed that HD patients may present difficulties in ToM abilities. Anyway, further studies are needed before any conclusions can be made.

Table 2 about here

6. Discussion

This review aimed at investigating ToM abilities in patients with neurodegenerative diseases. From the search in electronic databases, we found that ToM has been investigated in different

neurodegenerative diseases. Taken together, although the studies adopted different ToM tasks, they robustly provided evidence of a deficit of the cognitive ToM component in cortical (AD and clinical syndromes of the FTD spectrum) and frontal-subcortical (ALS and basal ganglia disorders) neurodegenerative diseases. As regards the affective ToM component, it resulted that it is markedly impaired in the clinical syndromes of the FTD spectrum; it also resulted that performances in tasks assessing this process are heterogeneous in PD and ALS, while no conclusion can be made on AD. We subsequently discuss these different patterns of ToM abilities in neurodegenerative diseases distinguishing different levels of analysis, i.e. neuropsychological, neuroanatomical, and neurochemical. As the large majority of the studies we found in literature concern AD, bvFTD, and PD, we mainly concentrate our analysis on these diseases.

6.1. Neuropsychological level

Although patients with different neurodegenerative diseases failed cognitive ToM tasks, their impaired performances probably had different neuropsychological correlates. As regards the relationship between cognitive functioning and ToM, executive functions (i.e. the control processes that allow a person to regulate one's thoughts and goal-directed behaviours) may play a crucial role.

Even though the nature of the relationship between executive functioning and ToM remains a subject of debate (e.g. Bird et al., 2004; Roca et al., 2011), studies on the emergence of ToM abilities help to understand the functional relationship that could link performance levels in executive tasks (especially of working memory and inhibitory control) and ToM tasks. In a series of works, Alan Leslie and colleagues (e.g. Friedman and Leslie, 2004; Leslie et al., 2004; 2005; Leslie and Polizzi, 1998) proposed a theoretical perspective according to which ToM abilities are based (1) on an innate and modular representational

system which spontaneously attends to behaviours and infers the mental states which contributed to them and (2) on a domain-general Selection Processing (SP) system which selects the specific mental state content to be attributed to a social agent in a given situation. As a person's beliefs typically are true, in normal (default) condition the modular representational system automatically attributes beliefs with contents that are true. On the contrary, in false-belief situations (such as in solving a false-belief task), to compute the content of the protagonist's belief about the correct location of an object, it is first necessary to inhibit the initial response based on the actual location. In these situations, the role of the SP system is crucial, as it is essentially a general executive process required to inhibit salient but unwanted responses. In other words, in some specific circumstances the false-belief task may be difficult because the inhibitory role of the SP is required to overcome the default 'true belief' attribution. According to several converging evidences, these specific circumstances are both the preschool period in which there is a gradual development of the PFC supporting the inhibitory processes involved in belief-desire reasoning (Leslie et al., 2004; 2005) and the cognitive aging in which there is a decline in a range of executive capacities including aspects of inhibitory function (Kramer et al., 1994; Raz, 2000).

In line with Leslie's theoretical proposal, German and Hehman (2006) demonstrated that compromised belief-desire reasoning in old age is the result of age-related decline in executive selection processes. Furthermore, more recently, Phillips and colleagues (2011) demonstrated that age differences in updating information in working memory have important influences on the specific problems encountered when reasoning about false beliefs in old age. In light of these considerations, we suggest that to comprehend the emerging scenario of the present review, it is necessary to take into account the normal age-related decline in executive functions and the way in which this decline affects ToM performance. Thus, the failure of AD, FTD, ALS patients, and patients with basal ganglia disorders in cognitive ToM

tasks may be at least partially explained on the basis of the executive dysfunction involving working memory and inhibitory control.

In bvFTD patients, either working memory or inhibitory control is slightly or clinically impaired since the early clinical stages (Krueger et al., 2009; Hornberger et al., 2008; Stopford et al., 2012); to date, few studies have investigated and found significant relationships between cognitive ToM and executive functions in bvFTD patients (e.g. Eslinger et al., 2007; Snowden et al., 2003). Considering the early marked and diffuse ToM impairment that characterizes bvFTD patients (e.g. Torralva et al., 2009), differently to the more progressive and subtle executive impairment (Hornberger et al., 2009), the assessment of bvFTD patients at similar stages of the disease could probably permit to better find significant correlations between ToM and executive functioning.

In PD patients, working memory is usually affected since the early clinical stages (Lee et al., 2010), while inhibitory control may be better preserved (Koerts et al., 2009). The different working memory load of the first- and second-order false-belief tasks could also explain the different performance levels of PD patients in these tasks. A verbal working memory impairment, which is associated with a set-shifting impairment, was only reported in one study we reviewed (Monetta et al., 2009), which showed that PD patients have ToM difficulties. Two recent studies reported that cognitive ToM performances significantly correlated with performances in the Frontal Assessment Battery (Santangelo et al., 2012), verbal fluency test, and card-sorting test (Yu et al., 2011). Other studies on PD reported executive deficits, but not correlation with performances in cognitive ToM tasks. In the study by Bodden et al. (2010), PD patients had lower performance than controls in a verbal fluency test but not in working memory tests, and executive performance did not correlate with performances in the cognitive ToM component of the Yoni task. Saltzman et al. (2000) reported executive difficulties of PD patients in fluency tasks and in a card-sorting test; Peron

et al. (2009) found that advanced PD patients achieved lower performance levels than early PD patients in a verbal fluency test. Resuming, the existence of an executive impairment could indirectly suggest that working memory and inhibitory control were also affected in these patients, and this could partially explain the difficulties these PD patients encountered in the cognitive aspects of ToM tasks.

In relation to AD patients, although they may present deficits in working memory (Huntley and Howard, 2010) and inhibitory control (Amieva et al., 2004), their failure in cognitive ToM tasks, mainly second-order false-belief tasks, is probably related and secondary to the diffuse cognitive impairment associated with dementia (Hodges et al., 2006), as suggested by the following empirical findings. Firstly, AD patients successfully perform cognitive ToM tasks with a minimal cognitive load, such as first-order false-belief tasks. Secondly, when AD is diagnosed, patients usually present deficits in (at least two) different cognitive domains that are necessary to perform ToM tasks, such as verbal episodic memory, working memory, and visuospatial functions. For example, in the study by Castelli et al. (2011), performances of AD patients in verbal ToM tasks correlated with cognitive measures of executive functions and of verbal episodic memory, and performances in ToM tasks supported by cartoons, correlated with cognitive measures of visuospatial abilities. Thirdly, in the studies by Zaitchik et al. (2004; 2006), AD patients failed in a similar way both cognitive ToM tasks and control condition tasks (not involving ToM abilities).

As regards the affective ToM component, it resulted that it is impaired in bvFTD patients and may be impaired in PD patients after some years of disease, while further studies are needed on AD. Neuropsychological evidence suggests that the orbitofrontal/ventromedial PFC plays a crucial role in affective ToM, as in other cognitive processes, such as decision-making and emotion-processing (Zald and Andreotti, 2010). Decision-making and emotion-processing have been investigated and reported as impaired in bvFTD and AD (Bediou et al.,

2009; Fernandez-Duque and Black, 2005; Gleichgerrcht et al., 2010); differently, these functions have been reported as preserved in the early clinical stages of PD (Poletti et al., 2010) and worsen with the progression of the disease, being impaired in more advanced stages (Assogna et al., 2009; Poletti et al., 2011b).

These neuropsychological findings are consistent with the hypothesis of a marked impairment of affective ToM in bvFTD since the early clinical stages (robustly confirmed) and a milder impairment of affective ToM in AD (to be confirmed); as regards affective ToM ability in PD patients, more heterogeneous and controversial findings emerged, considering that impaired performances have been reported after at least five years of disease duration (Bodden et al., 2010; Tsuruya et al., 2011), and preserved performances have been reported also after ten years of disease duration (Peron et al., 2009). However, globally considered, these findings are consistent with the hypothesis that affective ToM performances are slowly worsening in PD patients.

6.2. Neuroanatomical level

Recently the distinction between a cognitive component and an affective component of ToM has been boosted by the neuroanatomical–neurochemical model of ToM proposed by Abu-Akel and Shamay-Tsoory (2011; see Figure 2), which delineates the neuroanatomical and neurochemical systems involved in the representation of cognitive and affective mental states.

Figure 2 about here

According to this model, two distinct neural systems subtend cognitive and affective ToM. Each of these two systems can be divided into three main components: two mainly subcortical components (Cogn1 and Cogn2, Aff1 and Aff2; see Figure 2) and a mainly cortical component (connecting the posterior regions, which include both cognitive and affective ToM, the TPJ, STS, and PCC/PCun, with more anterior regions; Cogn3 and Aff3). Therefore, it could be hypothesized that in mainly cortical dementia, as AD and bvFTD, the cortical component of the ToM network (Cogn3 and Aff3) could be more impaired than the subcortical components (Cogn1 and Cogn2, Aff1 and Aff2, respectively), while basal ganglia diseases could present the opposite pattern.

Neuroanatomical evidence confirms the hypothesis that AD-related neuropathology involves structures of the more cortical component of the ToM network. Indeed, although in the early clinical stages of AD the neuropathology involves the medial temporal lobe (Singh et al., 2006), with the progression of the disease other cortical structures of the ToM network that allow the representations of another person's mental state (Bara et al., 2011; Ciaramidaro et al., 2007; Samson, 2010; Saxe and Wexler, 2005; Young et al., 2010), as the STS (Gomez-Isla et al., 1997), the TPJ (Harasty et al., 1999; Frisoni et al., 2005), and the PCC/PCun (Karas et al., 2007; Lehman et al., 2010; Shima et al., 2011) may be involved. In advanced AD stages, the cortical degeneration may involve also the prefrontal territories (Harwood et al., 2005; Naggara et al., 2006) involved in the Cogn3 and Aff3 components of the model of Abu-Akel and Shamay-Tsoory (2011); therefore, it could be hypothesized that ToM abilities worsen with progressive cortical diffusion of the AD-neuropathology.

Differently to AD, in the early clinical stages of bvFTD the cortical degeneration firstly involves the anterior cortical regions of the ToM network, particularly the ventromedial regions of the PFC (Hornberger et al., 2011; Peters et al., 2006); the progression of the disease also involves more posterior cortical areas of the ToM network (Diehl-Schmid et al., 2007),

including the STS (Zamboni et al., 2010) and the PCC/PCun (Du et al., 2007). Resuming, cortical neurodegenerative diseases as AD and bvFTD present neuroanatomical damages to structures of the mainly cortical components of the ToM network (Cogn3 and Aff3), with posterior regions (TPJ, STS, and PCC/PCun) more and earlier involved in AD and with anterior prefrontal regions (as the dorsolateral PFC, the ventromedial PFC, and the orbitofrontal cortex) more and earlier affected in bvFTD (Hornberger et al., 2010). Interestingly, the posterior regions of the ToM network are involved in the introspective mode used to represent self-mental states (Carruthers, 2009), and their disruption results in anosognosia (unawareness of disease), a commonly reported characteristic of AD and bvFTD patients (Salmon et al., 2006; 2008; Zamboni et al., 2010).

As regards PD, from the neuroanatomical perspective, the progressive striatal dopamine depletion has different effects on the functioning of the frontostriatal loops. According to the neuropathological staging proposed by Braak and colleagues (2003), in early PD (Braak stages 3 and 4), the dopamine depletion is greatest in the ventrolateral tier of the substantia nigra pars compacta, which projects primarily to the dorsal striatum (the dorsolateral putamen and the dorsal parts of the caudate nucleus), an area involved in the dorsolateral frontostriatal circuit, that includes the dorsolateral PFC, the striatum (dorsolateral caudate nucleus and dorsolateral putamen), the globus pallidus (dorsomedial), and the thalamus (Alexander et al., 1986; Kish et al., 1988; Middleton and Strick, 2001; Yeteran and Pandia, 1991). Dysfunction in this circuit impacts the executive functions based on the dorsolateral PFC (Cools et al., 2006), and, in particular, the impairment of the working memory could be the reason for the difficulties reported among these clinical populations in cognitive ToM tasks. With the progression of PD, dopamine depletion at the striatal level also impairs the functioning of the orbital loop that includes the orbitofrontal cortex, the striatum

(ventromedial caudate nucleus and ventral putamen), the globus pallidus (dorsomedial), and the thalamus.

Summarizing, in the early clinical stages of PD neurodegeneration involves the functioning of the Cogn1 and Cogn2 components of the cognitive ToM network, while the Aff1 and Aff2 components (mesocortical and mesolimbic DA systems) of the affective ToM network are better preserved. With the progression of the disease, these components of the affective ToM are also injured by neurodegeneration, and this suggests that affective ToM may be impaired in later stages of PD (Poletti et al., 2011c); however, only one study assessed the affective ToM component (Peron et al., 2009), with the RME and the FPR tasks in early and advanced PD patients, reporting no significant differences between patients at different stages of the disease. As regards the cortical component of the ToM network, it could be probably directly affected by PD-related neuropathology in advanced stages of the disease; as a matter of fact, these stages are characterized by a widespread cortical diffusion of Lewy body-related neuropathology (Braak et al., 2003; Kalaitzakis and Pearce, 2009), often resulting in a complex clinical picture with dementia and neuropsychiatric disturbances (Emre et al., 2007). Therefore, also the investigation of ToM in demented PD patients, in comparison to non-demented PD patients, deserves further studies.

6.3. Neurochemical level

The ToM model of Abu-Akel and Shamay-Tsoory (2011) also delineates the neurochemical systems involved in the representation of cognitive and affective mental states; in particular, reviewing the neuroimaging and pharmacological evidences in different clinical populations characterized by ToM deficits, this model focused on the role of the dopaminergic-serotonergic (DS) system (see Figure 2). In particular, the DS may be involved in the updating of short-term contextual representations by controlling the inflow of externally or

internally generated information (Brunet-Gouet and Decety, 2006), while the serotonergic system could modulate the dopaminergic system.

Neurochemical evidence shows that the DS system may be impaired by neurodegenerative processes. PD is considered the prototypical model of a dysfunctional dopaminergic system (Cools, 2006; Jankovic, 2008), with striatal dopamine depletion that initially involves the dorsolateral frontostriatal loop and progressively involves also the orbital frontostriatal loop; moreover, also the serotonergic system is early dysfunctional in PD (Beucke et al., 2010; Guttman, et al., 2007). However, although these findings suggest that the dysfunctional DS system of PD patients may contribute to their poor ToM performances, the only study (Peron et al., 2009) that assessed PD patients ‘on’ and ‘off’ dopaminergic therapy, reported no differences for all components (affective and cognitive) of ToM tasks. On the basis of these findings, the authors suggested that nigrostriatal and mesolimbic dopaminergic pathways do not contribute to ToM abilities. Another study (Roca et al., 2010) did not find significant differences between medicated and unmedicated early PD patients in the RME and the FPR tasks. However, no findings are available for performance levels of PD patients ‘on’ and ‘off’ dopaminergic therapy in cognitive ToM tasks only (e.g. false-belief tasks). Considering the importance of working memory for false-belief tasks with a demanding cognitive load (as second-order false-belief tasks) and the enhancing effects of dopaminergic drugs on working memory performances of PD patients (Costa et al., 2003; 2009), it could be argued that dopaminergic drugs may modulate the performances of PD patients more in cognitive ToM tasks than in affective ToM tasks. In sum, considering the spatiotemporal progression of dopamine depletion in PD patients and the effects of dopaminergic therapies on different frontostriatal circuits in diverse stages of PD, further studies with different tasks (both cognitive and affective) and with patients at diverse stages

of PD are needed to establish the influence of dopaminergic therapy on ToM functioning in the disease.

As regards AD, although the main dysfunction involves the acetylcholinergic system (Schliebs, 2005) and the glutamatergic system (Francis, 2005), preliminary findings suggest that catecholamines may be somehow dysfunctional in this clinical population (Madsen et al., 2011; Mitchell et al., 2011). As regards FTD, both the dopaminergic system and the serotonergic system may be dysfunctional (Bowen et al., 2008; Lanctot et al., 2007; Rinne et al., 2002), while the acetylcholine system appears relatively intact (Huey et al., 2006). These findings suggest that in cortical neurodegenerative diseases also, as AD and FTD, neurochemical alterations of neurotransmitter systems may be present and may contribute to ToM deficits.

7. Conclusion

This paper examined the findings on ToM abilities in neurodegenerative diseases; we found empirical evidence of different patterns of deficits in different diseases as regards both the cognitive and the affective components of ToM. We discussed these findings at three levels of analysis: neuropsychological, neuroanatomical, and neurochemical. Although the empirical literature on this topic begins to be enough robust to track some preliminary conclusions, some limitations emerged and further studies are needed in different directions. Firstly, although the prevailing view in the ToM literature is that the neural structures underlying cognitive and affective ToM, in particular the ones of the PFC, are functionally distinct, there is growing evidence that several structures play a prominent role in both functions, and in fact the traditional distinction between cognitive and affective processes has been questioned (e.g. Pessoa, 2008; Tamietto et al., 2006; 2007). Thus, future research should take into consideration this caveat in their theoretical and methodological framework. Secondly, more

studies are needed on neurodegenerative diseases scarcely investigated, especially ALS, clinical syndromes of the FTD spectrum (such as progressive non-fluent aphasia and semantic dementia), corticobasal degeneration, progressive supranuclear palsy, and dementias associated with Lewy Body neuropathology such as Parkinson's Disease dementia and Lewy Body dementia. Thirdly, as regards AD, it could be interesting to investigate ToM abilities in the prodromal clinical phases, as it could be considered the clinical picture of amnesic mild cognitive impairment (Wilson et al., 2011). Finally, cognitive and affective processes somehow related to ToM, such as empathy, moral judgement, lie detection, and sarcasm understanding, have been preliminarily investigated in neurodegenerative diseases (Calabria et al., 2009; Kipps et al., 2009; Kosmidis et al., 2008; Mendez et al., 2005; Rankin et al., 2005; Shany-Ur et al., 2011), and further studies are needed to understand how these processes are impaired and which role is played by the dysfunctional ToM abilities.

Despite such limitations, the findings presented here provide evidence of compromised ToM abilities in neurodegenerative diseases and strongly support the opportunity to introduce validated ToM tasks in the neuropsychological assessment of such diseases.

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Figures captions

Figure 1. A model with two neural systems for cognitive and affective ToM processing with different and common brain areas involved.

Figure 2. A model of ToM processing which delineates the neuroanatomical and neurochemical networks involved in the representation of cognitive and affective mental states (adapted from Abu-Akel and Shamay-Tsoory, 2011).

Abbreviations: Amy = Amygdala; Caud = Caudate nucleus; dACC = dorsal anterior cingulate cortex; DLPFC = dorsal lateral prefrontal cortex; dMPFC = dorsal medial prefrontal cortex; DRN = Dorsal raphe nucleus; DS = Dopaminergic-Serotonergic; dTP = dorsal temporal pole; ILFC = inferolateral frontal cortex; MRN = Medial raphe nucleus; NAc = Nucleus accumbens; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; PCun = precuneus; Put = Putamen; SN = Substansia nigra; STS = superior temporal sulcus; TPJ = temporo-parietal junction; vACC = ventral anterior cingulate cortex; vMPFC = ventral medial prefrontal cortex; VP = Ventral pallidum; VTA = Ventral tegmental area; vTP = ventral temporal pole.

Figure 1

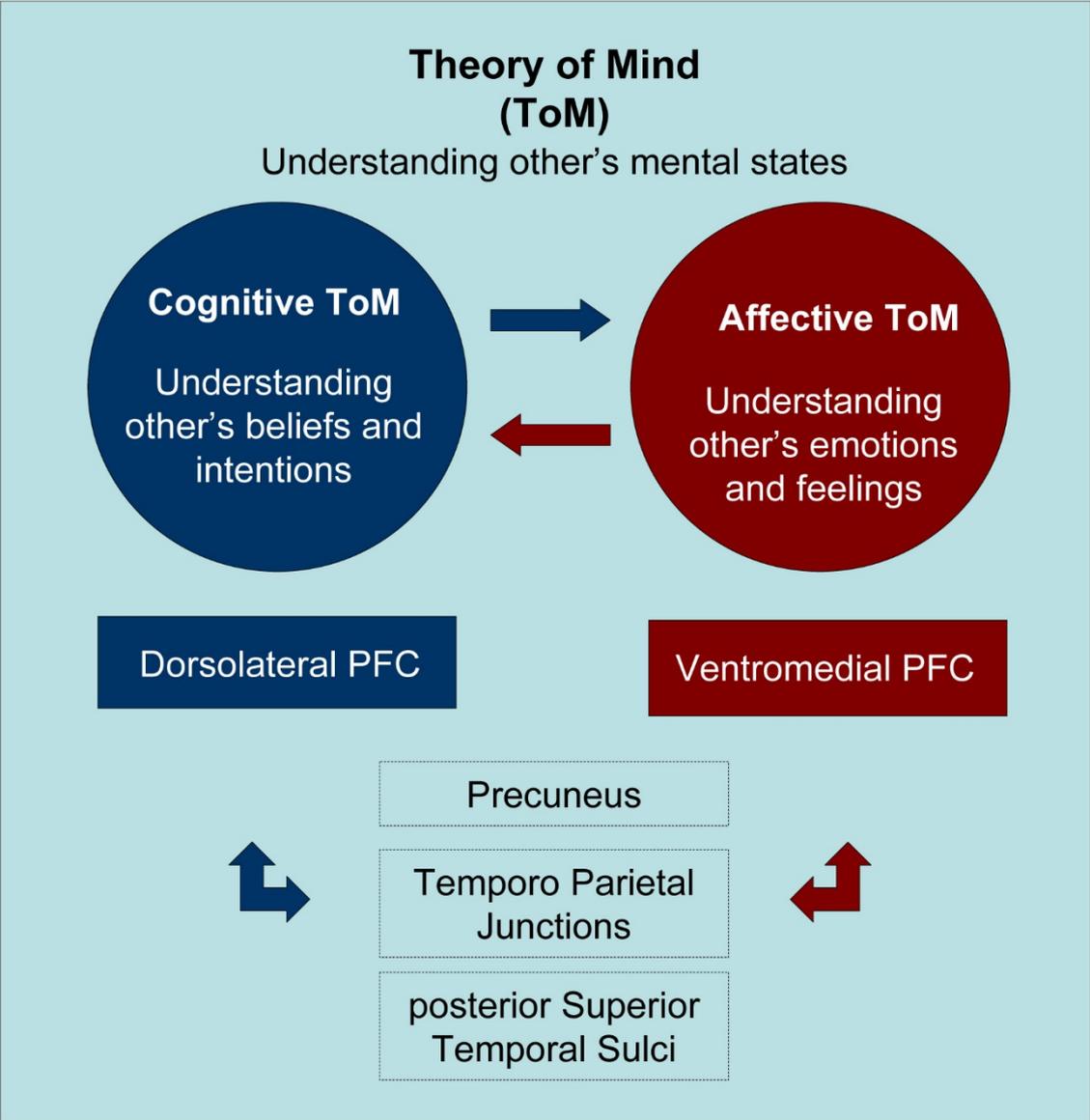


Figure 2

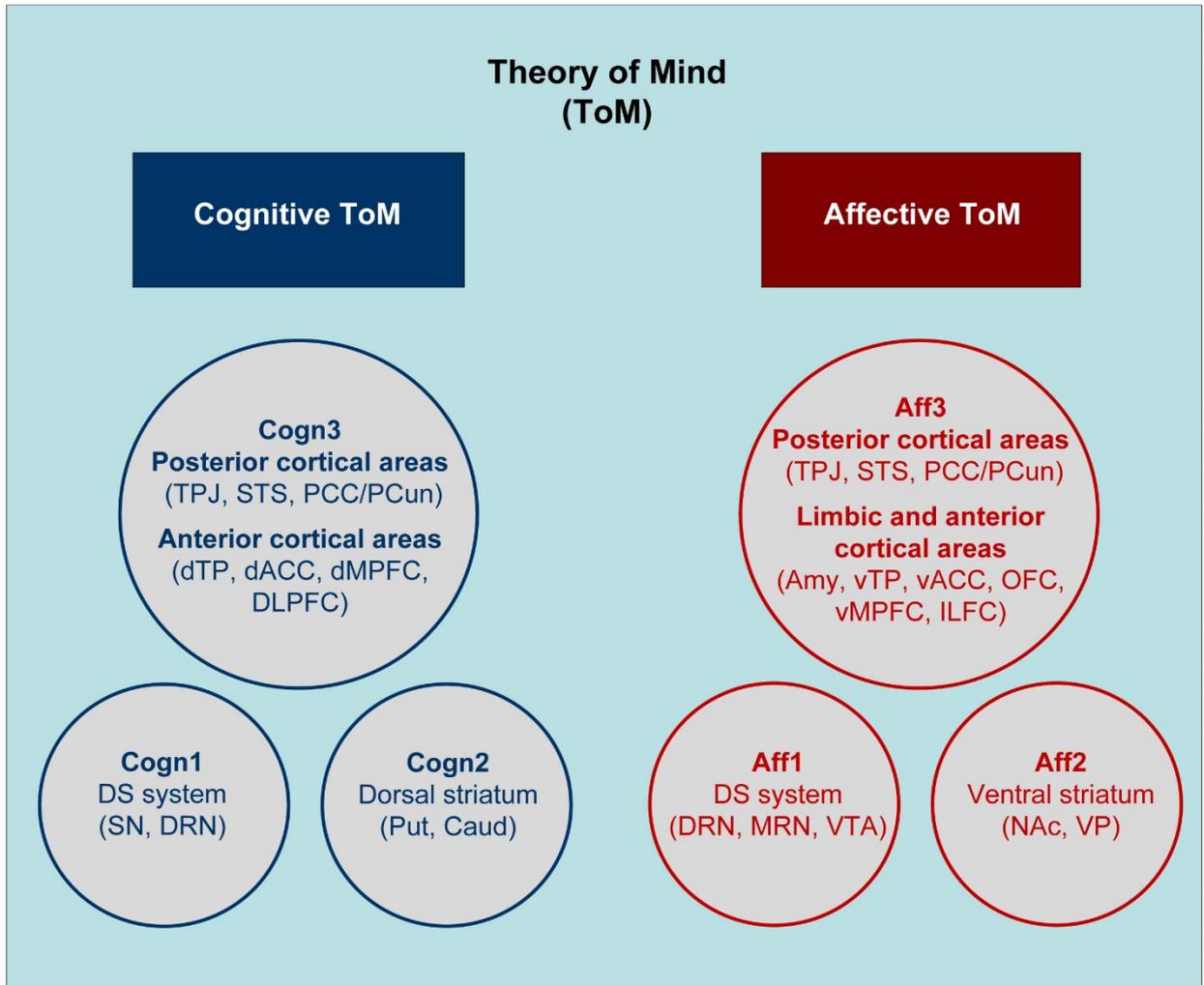


Table 1. Studies including Theory of Mind tasks in patients with Alzheimer’s disease, frontotemporal dementia, amyotrophic lateral sclerosis or progressive supranuclear palsy. The order is chronological.

Neurodegenerative disease	Authors	Sample (n)	Patients’ Mean age in years (SD)	Sex M/F	MMSE (SD)	ToM Task	ToM ability	ToM results
Alzheimer’s disease	Cuerva et al., 2001	34 AD 10 HC	N/A 60.6 (2.3)	11/23 4/6	N/A N/A	Second-order FBT	Cognitive	Impaired
	Gregory et al., 2002	12 AD 16 HC	66.5 (8.9) 57.1 (5.1)	6/6 8/8	27.1 (1.7) 28.7 (1.0)	First-order FBT Second-order FBT FPR RME	Cognitive Cognitive Cognitive and Affective Affective	Preserved Impaired Preserved Preserved
	Zaitchik et al., 2004	25 AD 15 HC	88.96 (5.75) 88.47 (6.7)	2/13 2/23	19.5 (3.50)* 28.9 (1.28)	False belief/Real object task False belief/False picture story	Cognitive Cognitive	Preserved Partially impaired
	Zaitchik et al., 2006	20 AD 20 HC	Range of both AD and HC 69-94	7/13 4/16	24.0 (3.1) 29.5 (0.7)	First-order inferences tasks Second-order inferences tasks	Cognitive Cognitive	Preserved Partially impaired
	Verdon et al., 2007	20 AD 20 HC young 20 HC elderly	82 (5.25) 27 (5.75) 82 (4.52)	6/14 9/11 8/12	23 (3.72) N/A 29 (0.54)	Attribution of Intention	Cognitive	Impaired
	Fernandez-Duque et al., 2009	17 AD 12 HC	69.4 (5.7) 68.7 (8.8)	11/6 6/6	24.9 (2.1)* 28.8 (0.8)	First-order FBT Second-order FBT	Cognitive Cognitive	Preserved Impaired
	Youmans and Bourgeois, 2010	10 AD 10 HC	82 (6.15) 78 (6.11)	2/8 4/6	20.6 (1.83)* 29.8 (0.42)	First-order FBT Second-order FBT	Cognitive Cognitive	Partially preserved Mild impaired
	Castelli et al., 2011	16 AD 16 HC	70.5 (5.71) 71.38 (3.65)	6/9 3/13	23.69 (2.05)* 29.19 (1.27)	Eye Direction Detection Emotion–situation understanding First-order FBT Second-order FBT RME Strange Stories	Cognitive Affective Cognitive Cognitive Affective Cognitive and Affective	Preserved Preserved Partially preserved Impaired Impaired Impaired

Behavioral variant
of frontotemporal
dementia

Funkiewiez et al., 2012	22 AD/aMCI 30 HC	68.6 (11.1) 66.2 (10.0)	14/8 13/17	25.0 (2.4)* 29.0 (0.8)	FPR	Cognitive and Affective	Preserved
Shany-Ur et al., in press	32 AD 77 HC	62.3 (9.1) 68.2 (8.9)	17/15 32/45	24.4 (3.0)* 29.4 (0.9)	First and second-order FBT Social Inferences	Cognitive Cognitive	Impaired Preserved
Lough et al., 2001	Single-case bvFTD	47	1/0	29	First-order FBT Second-order FBT FPR RME	Cognitive Cognitive Cognitive and Affective Affective	Impaired Impaired Impaired Preserved
Gregory et al., 2002	19 bvFTD 16 HC	58.6 (6.9)* 57.1 (5.1)	16/3 8/8	26.6 (3.2) 28.7 (1.0)	First-order FBT Second-order FBT FPR RME	Cognitive Cognitive Cognitive and Affective Affective	Impaired Impaired Impaired Impaired
Lough and Hodges, 2002	Single-case bvFTD	57	1/0	29	First-order FBT Second-order FBT FPR RME	Cognitive Cognitive Cognitive and Affective Affective	Impaired Impaired Impaired Impaired
Snowden et al., 2003	13 bvFTD 18 HC	60 (7) 49 (23)	9/4 8/10	22 (6.0) N/A	ToM cartoons ToM stories Judgment of Preference	Cognitive Cognitive Cognitive	Impaired Impaired Impaired
Lough et al., 2006	18 bvFTD 13 HC	61.1 (6.7) 57 (9.1)	16/2 9/4	28 (2.8) N/A	ToM cartoons ToM stories	Cognitive Cognitive	Impaired Impaired
Eslinger et al., 2007	12 bvFTD 17 HC	66.17 75.07	N/A N/A	22.58* 29.33	First-order FBT Second-order FBT	Cognitive Cognitive	Impaired Impaired
Torralva et al., 2007	20 bvFTD 10 HC	67.2 (8.1) 63.5 (5.8)	11/9 4/6	27.9 (1.6)* 29.5 (0.8)	FPR RME	Cognitive and Affective Affective	Impaired Impaired
Fernandez-Duque et al., 2009	11 bvFTD 12 HC	60.6 (7.2)* 68.7 (8.8)	8/3 6/6	26.4 (1.6)* 28.8 (0.8)	First-order FBT Second-order FBT	Cognitive Cognitive	Preserved Impaired
Torralva et al., 2009	16 highACE bvFTD 19 lowACE bvFTD 14 HC	65.0 (7.4) 69.1 (5.7) 65.5 (6.5)	7/9 9/10 7/7	28.2 (1.9) 25.7 (3.2)* 29.2 (1.0)	FPR RME	Cognitive and Affective Affective	Impaired Impaired

	Gleichgerrcht et al., 2011	13 bvFTD – No** 9 bvFTD – Yes**	71.4 (5.46) 71.2 (6.80)	8/5 3/6	22.7 (5.96) 23.2 (4.32)	FPR RME	Cognitive and Affective Affective	No group = Yes group No group > Yes group
	Poletti et al., 2011	Single-case bvFTD	57	1/0	26	RME	Affective	Impaired
	Funkiewiez et al., 2012	22 bvFTD 30 HC	65.5 (10.3) 66.2 (10.0)	17/5* 13/17	25.8 (2.5)* 29.0 (0.8)	FPR	Cognitive and Affective	Impaired
	Shany-Ur et al., in press	39 bvFTD 77 HC	61.6 (7.3) 68.2 (8.9)	26/13 32/45	25.7 (3.0)* 29.4 (0.9)	First and second-order FBT Social Inferences	Cognitive Cognitive	Impaired Impaired
Progressive supranuclear palsy	Shany-Ur et al., in press	16 PSP 77 HC	66.9 (5.1) 68.2 (8.9)	8/8 32/45	26.8 (1.9) 29.4 (0.9)	First and second-order FBT Social Inferences	Cognitive Cognitive	Preserved Impaired
Semantic dementia and progressive nonfluent aphasia	Eslinger et al., 2007	14 APH 17 HC	71.92 75.07	N/A N/A	23.45* 29.33	First-order FBT Second-order FBT	Cognitive Cognitive	Impaired Impaired
	Duval et al., 2012	15 SD 36 HC	64.27 (6.53) 64.14 (8.25)	6/9 12/24	118 (9.57) 139.05 (4.38) on MDRS	<i>Objective ToM</i> Attribution of Intention First and second-order FBT RME ToM's taste <i>Subjective ToM</i> Cognitive ToM Scale Affective ToM Scale	Cognitive Cognitive Affective Affective	Impaired Impaired Impaired Impaired Preserved
Amyotrophic lateral sclerosis	Gibbons et al., 2007	16 ALS 16 HC	62 (0.1) 58 (0.8)	10/6 7/9	28 (2) 28 (2)	ToM cartoons ToM stories	Cognitive Cognitive	Preserved Impaired
	Meier et al., 2010	18 ALS 18 HC	64.50 (11.5) 63.56 (9.5)	12/6 11/7	N/A	FPR	Cognitive and Affective	Impaired

Cavallo et al., 2011	15 ALS 21 HC	59.07 (17.6) 57.48 (12.9)	11/4 14/7	N/A	Understanding social stories Understanding non-social stories RME	Cognitive Cognitive Affective	Impaired Preserved Preserved
Girardi et al., 2011	14 ALS 20 HC	57.4 (16) 54.8 (11.5)	10/4 15/4	N/A	Judgment of Preference RME	Cognitive Affective	Impaired Mild impaired

ACE = Addenbrooke's Cognitive Examination; AD = Alzheimer's Disease; ALS = Amyotrophic Lateral Sclerosis; aMCI = amnesic Mild Cognitive Impairment; AD = Alzheimer's Disease; APH = Subgroup of FTD Patients with Progressive Non-fluent Aphasia or Semantic Dementia; bvFTD = behavioural variant of Frontotemporal Dementia; FBT = False Belief Task; FPR = Faux Pas Recognition; HC = Healthy Controls; MDRS = Mattis Dementia Rating Scale; MMSE = Mini Mental State Examination; N/A = Not Available; PSP = Progressive Supranuclear Palsy; RME = Reading the Mind in the Eyes Test; SD = Semantic Dementia; ToM = Theory of Mind.

* The difference is statistically significant compared to HC

** BvFTD patients were divided into two groups depending on their answer to a personal dilemmatic judgment, the Footbridge moral dilemma:

YES patients said they would push the man into the tracks; NO patients said they would not push him.

Table 2. Studies including Theory of Mind tasks in patients with Parkinson's disease or Huntington's disease. The order is chronological.

Neurodegenerative disease	Authors	Sample (n)	Patients' Mean age in years (SD)	Sex M/F	MMSE (SD)	ToM Task	ToM ability	ToM results
Parkinson's disease	Saltzman et al., 2000	11 PD 8 HC	71 (13.45) 71.61 (9.42)	6/5 3/5	Above 26 Above 26	First and second-order FBT Spy task Perspective taking Deception task	Cognitive Cognitive Cognitive Cognitive	Impaired Impaired Preserved Preserved
	Mengelberg and Siegert, 2003	13 PD 11 HC	72.9 (8.9) 75.45 (1.69)	4/9 5/6	28.46 (1.39) 29.18 (1.17)	Card-sequencing false beliefs ToM stories First-order FBT Second-order FBT	Cognitive Cognitive Cognitive Cognitive	Impaired Impaired Impaired Preserved
	Mimura et al., 2006	18 PD 20 HC	68.9 (7.0) N/A	5/13 4/16	27.8 (1.9) 28.9 (1.6)	RME	Affective	Mild impaired
	Kawamura and Koyama, 2007	11 PD 20 HC	67.1 68	3/8 16/4	28.1 (2.6) N/A	FPR	Cognitive and Affective	Impaired cognitive component
	Euteneuer et al., 2009	21 PD 23 HC	67.6 (7.31) 64.4 (8.56)	7/14 12/11	29 (1.10)* 29.65 (0.65)	RME	Affective	Preserved
	Monetta et al., 2009	11 PD 11 HC	67.1 (10.9) 71.2 (7.8)	5/6 5/6	139.2 (2.5) 140.3 (2.9) on MDRS	First-order FBT Second-order FBT	Cognitive Cognitive	Mostly preserved Impaired
	Peron et al., 2009	17 early PD 26 HC	61.0 (7.1) 59.8 (6.8)	5/12 13/13	138.8 (4.4) Early PD On 140 (4.5) Early PD Off 139.1 (4.1) Advanced PD on MDRS	RME FPR	Affective Cognitive and Affective	Preserved Preserved
		27 advanced PD 26 HC	56.6 (7.8) 59.8 (6.8)	18/9 13/13	28.9 (0.8) HC on MMSE	RME FPR	Affective Cognitive and Affective	Preserved Impaired cognitive component
	Bodden et al., 2010	21 PD 21 HC	63.7 (10.0) 58.5 (10.2)	15/6 15/6	29 (Range 28-30) 30 (Range 28-30)	RME Affective First-order Yoni Cognitive First-order Yoni Affective Second-order Yoni Cognitive Second-order Yoni	Affective Affective Cognitive Affective Cognitive	Impaired Preserved Preserved Impaired Impaired

	Peron et al., 2010	13 PD 13 HC	53.3 (8.5) Pre-DBS N/A Post-DBS N/A HC	8/5 8/5	141.4 (1.7) Pre-DBS 141.1 (1.9) Post-DBS 141.2 (1.9) HC on MDRS	RME	Affective	Pre-DBS Preserved Post-DBS Impaired
	Roca et al., 2010	16 Medicated PD 35 HC	63.4 (8.47) 60.4 (11.6)	N/A N/A	29.00 (1.55) N/A	RME FPR	Affective Cognitive and Affective	Preserved Impaired cognitive component
		20 Drug free (Unmedicated) PD 35 HC	63.5 (11.8) 60.4 (11.6)	N/A N/A	28.26 (1.45) N/A	RME FPR	Affective Cognitive and Affective	Preserved Impaired cognitive component
	Tsuruya et al., 2011	20 PD 20 HC	70.5 (8.6) 67.7 (4.5)	11/9 11/9	28.3 (1.6) 28.6 (2.0)	RME	Affective	Impaired
	Santangelo et al., 2012	33 PD 33 HC	62.7 (10.5) 62.4 (10.6)	22/11 22/11	27.9 (1.3) 27.8 (1.3)	Strange Stories Emotion Attribution Task	Cognitive Affective	Impaired Impaired
	Yu et al., 2012	39 PD 40 HC	62.7 (4.2) 61.9 (9.3)	25/14 20/20	27.9 (1.8) 27.9 (2.0)	FPR ToM cartoons ToM stories	Cognitive and Affective Cognitive Cognitive	Preserved Impaired Preserved
Huntington's disease	Snowden et al., 2003	13 HD 18 HC	50 (7) 49 (23)	5/8 8/10	25 (3) N/A	ToM cartoons ToM stories Judgment of Preference	Cognitive Cognitive Cognitive	Impaired Impaired Preserved
	Brune et al., 2011	25 HD 25 HC	47.8 (11.8) 44.6 (10.6)	12/13 10/15	N/A N/A	ToM sequencing ToM questionnaire (First and Second-order)	Cognitive Cognitive	Impaired Impaired
	Allain et al., 2011	18 HD 18 HC	50.7 (8.8) 47.7 (8.9)	10/8 11/7	25.4 (1.8) N/A	Attribution of Intention RME	Cognitive Affective	Impaired Impaired

DBS = Deep Brain Stimulation; FBT = False Belief Task; FPR = Faux Pas Recognition; HC = Healthy Controls; HD = Huntington's Disease; MDRS = Mattis Dementia Rating Scale; MMSE = Mini Mental State Examination; N/A = Not Available; PD = Parkinson's Disease; PSP = Progressive Supranuclear Palsy; RME = Reading the Mind in the Eyes; ToM = Theory of Mind.

* The difference is statistically significant compared to HC