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***curriculum* "Persona, Sviluppo e Apprendimento: prospettive teoriche, epistemologiche e applicative"**
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S.S.D: M-PSI/04-08

COGNITIVE AND AFFECTIVE THEORY OF MIND IN NORMAL AGING AND NEURODEGENERATIVE DISEASES

Tesi di Dottorato di: Federica ROSSETTO

Matricola: 4412077

Anno Accademico 2017/2018

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Chapter 1

General Introduction

COGNITIVE AND AFFECTIVE THEORY OF MIND IN NORMAL AGING AND NEURODEGENERATIVE DISEASES

Theory of Mind: a key aspect of Social Cognition

"We are an essentially social species" (Adolphs, 2009). Much of our behavior in everyday life is motivated by social goals, since the early stage of infancy. For that reason, the human's social cognition constitutes a crucial neurocognitive ability, which continues to develop across the entire life-span. It consists of all the psychological processes that subserve social behavior, allowing us to process and interpret social information, such as intentions, feelings, and thoughts of other people (Adolphs, 2009).

Firstly, social cognition has been studied in social animals (including primates) as the ability to exchange signals between conspecifics in order to understand and predict other's behavior (Adolphs et al., 2009). In this theoretical framework, it was assumed that human social cognition includes all the processes used by other social animals, since human social behavior arises from neurobiological and psychological systems shared with other mammalian species. However, other psychological processes appear to be specific for the human species (Frith and Frith, 2007), such as the ability of individuals to understand conspecifics as beings *like themselves*, with intentions, belief, and desires like their own (Tommasello, 1999).

Currently, social cognition is defined as a multi-componential construct which includes different abilities, some specific to the social domain, and other more general and involved in emotional and reward processing. A recent model proposed by Henry and colleagues (2016) focused on four social cognitive domains, which operate in parallel during the complex real-life situations: emotional empathy (the emotional response to the perceived situations of others), social perception (the process by which we form impressions of other people and make inferences about them), social behavior (the behavior directed towards other people) and Theory of Mind (ToM, the ability to understand other's mental states) (Henry et al., 2016).

ToM, also called "mentalization"[1] (Fonagy, 2004), represents one of the most researched aspects of social cognition, which refers to the ability to understand, explain and predict own and other's behaviors on the basis of complex mental states such as beliefs and desires (Premack & Woodruff, 1978). It is now widely established that ToM constitutes a complex, multidimensional construct requiring the integration of cognitive (*cold*) as well as affective (*hot*) ToM processing (Brothers & Ring, 1992; Shamay-Tsoory et al., 2005; Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Aharon-Peretz & Levkovitz, 2007; Shamay-Tsoory et al., 2010; Wang & Su, 2013). Specifically, cognitive ToM represents the ability to understand intentions, beliefs, and thoughts of self and others, while affective ToM concerns reasoning about own and other's affective states, emotions or feelings.

Over the last two decades, cognitive and social neuroscience research have concentrated their efforts in identifying networks of cortical and subcortical brain regions specifically dedicated to represent cognitive and affective mental states to both self and other, showing that both dimensions of ToM could be mediated by at least partially dissociated networks (Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory et al., 2005; Hynes et al., 2006; Völlm et al., 2006). The neurobiological model proposed by Abu-Akel and Shamay-Tsoory (2011) assumed that cognitive and affective dimensions of ToM are subserved by dissociable and interacting networks. In particular, the cognitive ToM network primarily involves the dorsomedial prefrontal cortex, the dorsal anterior cingulate cortex, and the dorsal striatum, while the affective ToM network mainly engages the ventromedial and orbitofrontal cortices, the ventral anterior cingulate cortex, the amygdala, and the ventral striatum (Abu-Akel & Shamay-Tsoory, 2011).

Given the functional independence of cognitive and affective mental states, appropriate ToM measures are available to explore both dimensions of ToM. For example, the cognitive dimension of ToM can be evaluated through 1) The *First-order false belief task* (Baron-Cohen, Leslie, & Frith, 1985; Wimmer & Perner, 1983), which evaluates the first level of recursive thinking (i.e. "I think that you think"), and the *Second-order false belief task* (Baron-Cohen, 1989; Perner & Wimmer, 1985), which assess the second level of recursive thinking (i.e. 'I think that you think that she/he thinks'); 2) the cognitive sub-component of the *Faux Pas Recognition tes*t (Stone, Baron-Cohen, & Knight, 1998), defined as a situation in which "a speaker says something without considering if it is something that the listener might not want to hear or know, and which typically

[1] In this thesis, "Theory of Mind" and "mentalization" will be used interchangeably. However, it should be noted that the term "mentalization" includes both cognitive (traditionally detected by the classical ToM tasks, such as the False Belief task) and emotional-affective meanings (Allen et al., 2010).

has negative consequences that the speaker never intended” (Baron-Cohen et al., 1999, p. 408); and 3) the *Strange Stories task*[2] (Happè, 1994), which assess a more advanced level of ToM reasoning about the social world. On the other hand, affective ToM is commonly evaluated using: 1) the *Reading the Mind in the Eyes test* (Baron-Cohen et al., 2001), which evaluates the ability to infer the affective mental state from the eye region of the human face; and 2) the affective subcomponent of the *Faux Pas Recognition test* described above (Stone, Baron-Cohen, & Knight, 1998). Each studies included in this thesis will evaluate, in age-related pathologies, both cognitive and affective mentalizing abilities through some of the conventional ToM tasks mentioned above, and in particular:

- The *Deceptive Box Task* (Perner, Leekam, & Wimmer, 1987), which is a first-order false belief task. In this task, a closed box of candies is shown, the content of which has been previously substituted with staples. The examiner asks participant what the closed box contains; then, the real content is shown and the box is closed again. In the end, the participant is asked to predict what another person would say if shown that closed box, and to say what he/she had thought before discovering the real content;
- The *Look-Prediction* and the *Say-Prediction* tasks (Astington, Pelletier, & Homer, 2002; Liverta Sempio et al., 2005; Sullivan, Zaitchik, & Tager-Flusberg, 1994) assess the second level of false belief understanding (second-order false belief tasks). The participant has to predict where a character in the story thinks another character would look for a hidden object (look-prediction) or what a character thinks the other one would say about a hidden object (say-prediction).
- The *Reading the Mind in the Eyes test* (RME test, Baron-Cohen et al., 2001) assesses the affective component of ToM. Participants have to infer the mental state of a character of which only the eye region is visible, choosing the word that describes what the character is feeling or thinking from four mental states written under each picture. The “Gender test” is also used as a control task.

[2] In this thesis, “Cognitive ToM” is defined as the ability to understand intentions, beliefs, and thoughts of self and others (Brothers & Ring, 1992; Shamay-Tsoory et al., 2005). Research which relies on this definition generally included the Strange Stories task among the cognitive ToM tasks, since it requires the attribution of thoughts, belief, and intentions (Poletti et al., 2012; Duval et al., 2011; Kemp et al., 2012; Charlton et al., 2009). In particular, the review by Poletti and colleagues (2012) states: " 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" (Poletti et al., 2012; p.2149).

- The *Strange Stories* task (Happè, 1994; Happè, Brownell, & Winner, 1999) assess an advanced level of ToM reasoning. A selection of four physical stories is also used as a control condition.

Moreover, in Chapter 4, the conventional ToM tasks (the Deceptive Box task, the Look Prediction and the Say Prediction tasks, the Strange Stories task, and the Reading the Mind in the Eyes test) will be accompanied by a computerized ToM task which investigates simultaneously each aspects of ToM (cognitive and affective), at different inferential levels (both first- and second-order mental state attributions): the *Yoni task* (Shamay-Tsoory & Aharon-Peretz, 2007). It consists of 98 trials showing a face named "Yoni" ("Gianni" in the Italian version) and four colored pictures around the face referring to different semantic categories or faces. The participant is required to choose the correct picture to which Yoni is referring based on a sentence that appears on the top of the screen and on specific cues, such as the Yoni's eye gaze and the facial expression or the eye gaze/facial expression of faces around him. The items differ in the complexity of the attribution (i.e., first- or second-order levels) and in the affective (*Yoni likes*…), cognitive (*Yoni is thinking* of…) or physical (*Yoni is close to*…) characterizations. The innovative aspect introduced by this task concern the opportunity to evaluate the ability to judge first- and second-order, affective and cognitive mental state attributions according to simple verbal instructions and eye-gaze cues, thus involving minimal language and executive demands (Shamay-Tsoory & Aharon-Peretz, 2007).

Theory of Mind in the life-span perspective

The development of ToM follows a specific evolutionary path starting from the early stages of infancy. Wellman, Cross, & Watson (2001) proposed that this ability is absent in children before 4 years of age. However, more recent research demonstrated that even 13-15 months-old infants have an implicit understanding of mental states (Surian, Caldi, & Sperber, 2007; Onishi & Baillargeon's, 2005). Subsequently, the ToM acquisition proceeds in a hierarchic way (Wellman, 2011), with the understanding primarily of simple mental states (such as emotions and intentions of other people). Gradually, in deeper connection with the increase of social relationships, pre-scholar children (around 4-5 years old) comes to understand more complex mental contents, such as the first level of false belief attribution (Wimmer & Perner, 1983). The "False Belief task' (Perner & Wimmer, 1985) has been developed with the specific purpose to test the evolution of ToM in childhood, and, in particular, the acquisition of the false belief concept and of the recursive thinking ability. The *First order false belief task* (Baron-Cohen, Leslie, & Frith, 1985; Wimmer & Perner, 1983) evaluates the first level of recursive thinking (i.e. "I think that you think"), while the *Second* *order false belief task* (Baron-Cohen, 1989; Perner & Wimmer, 1985) assess the second level of recursive thinking (i.e. 'I think that you think that she/he thinks'), which emerged at around 8 years of age (Perner & Wimmer, 1985).

The development of ToM competencies continue beyond childhood. In fact, a growing body of research found significant changes in the ToM performance in adolescence and in early adulthood (Sommerville et al., 2013; Dumontheil et al., 2010; Apperly et al., 2012). In the last few years, the focus of attention has been directed also towards the investigation of the evolution of ToM in successful and unsuccessful neurocognitive aging.

Theory of Mind in successful and unsuccessful aging

In recent years, there is growing interest in the evolution of ToM in the life-span perspective, especially in later life (for a review, see Moran et al., 2013). Individual differences in social cognitive functioning have significant implications for social interactions in old age since they have been associated with a reduction in social participation, loneliness and mental health problems (Bailey et al., 2008; Henry et al., 2013).

An initial wave of studies investigated the effect of typical (successful) aging on ToM ability. Experimental research in this field highlighted a complex, multifaceted picture of gain and loss, with specific aspects of ToM more vulnerable to the effect of aging, while other components seem to be preserved over the years.

In the first study in older people, Happé, Winner, & Brownell (1998) found an age-related improvement of ToM abilities evaluated through the Strange Stories task. However, these results were not replicated in the following research. In contrast, a number of studies (for a review, see Henry et al., 2013) found that older people were selectively impaired on the more cognitively demanded ToM tasks, such as the second-order false belief tasks (compared to the first-order ones) and the verbal story tasks (compared to the visual ones). This observed selective impairment in the more complex ToM tasks has been explained by the age-related decline in cognitive functioning (Moran et al., 2013). However, ToM deficit has been detected even in tasks with reduced cognitive load, such as the RME test (Duval et al., 2011; Pardini & Nichelli, 2009; Phillips et al., 2002), suggesting that the ToM construct is at least partially independent from other cognitive functions.

To address this issue, several studies investigated changes of mentalizing abilities focusing on both cognitive and affective dimensions of ToM. Overall, an age-related decline in cognitive ToM has been detected from the majority of studies using the Strange Stories task or other second order false belief tasks (Cavallini et al., 2013; Bernstein et al., 2011; Phillips et al., 2011; Charlton et al., 2009; Sullivan & Ruffman, 2004; Maylor et al., 2002), while no age differences emerged in the first order ToM tasks (Slessor et al., 2007; McKinnon and Moscovitch, 2007). More heterogeneous findings emerged considering the affective ToM, showing both a preservation (Castelli et al., 2010; Phillips et al., 2002; Phillips, MacLean & Allen, 2002; MacPherson et al., 2002) and an impairment (Pardini & Nichelli, 2009; McKinnon & Moscovitch, 2007; Slessor et al., 2007; Sullivan & Ruffman, 2004) in this ability (for a recent overview on this topic, see Henry et al., 2013).

Such mixed results emerged also from studies considering both cognitive and affective ToM simultaneously. Duval et al. (2011) and Rakoczy et al. (2012) found that both cognitive and affective dimensions were affected by the aging process, while Wang and Su (2013) and Li et al. (2013) reported a worse performance in older people compared to younger ones only in cognitive ToM. Such discrepancy between studies probably reflects differences in the tasks used and different modalities of presentation of the same task (i.e. visual or verbal modality), which involves a different level of cognitive load.

The meta-analysis of Henry and colleagues (2013) has made an important contribution to clarify the contradictory findings related to nature and magnitude of age-related differences in ToM performance, highlighting that "a remarkably consistent picture of impairment emerges, with older adults significantly poorer than their younger counterparts across all measures assessed" (Henry et al., 2013, p.832). Thus, the age-related decline in ToM performance goes beyond the multiple operationalizations of this construct and the differences in the methodologies implied by each study. Moreover, the impairment of this social competence may not be ascribed only to general cognitive functioning in older adults but could represent a primary deficit in understanding complex mental states and emotions, since it is at least partially independent from a more general cognitive or executive decline.

In parallel with the research in normal aging, an increasing number of studies have been developed focusing on ToM performance in pathological (unsuccessful) aging, which is the focus of this dissertation. Recently, it has been proposed that failures in cognitive and affective dimensions of ToM may constitute salient features of many age-related pathological conditions, leading to impairments in social functioning and poor quality of life (Cotter et al., 2017). The most recent edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) introduced social cognition as one of the six core aspects of neurocognitive functioning and upholds the importance of the social cognitive assessment in the clinical practice, in addition to the standard neuropsychological assessment. Thus, it may be of particular interest to explore the pattern of cognitive and/or affective mentalizing impairment in people with neurodegenerative conditions, with the purpose to better define the theoretical framework for the age-related decline of social competences.

Theory of mind in the clinical practice: differential impairment of cognitive and affective ToM in neurodegenerative pathologies

It has been assumed that patients with different neurodegenerative diseases may show a different pattern of ToM impairment according to how the neuropathological process affect the neural circuits underlying ToM during the progression of the disease (Poletti et al., 2012). Moreover, cognitive and affective components of ToM may be affected differently on the basis of the specific neurodegenerative condition and the disease's stage considered. The Chapter 4 of the present dissertation is focused on the comparison between two non-demented neurodegenerative pathologies: the early stage of Parkinson's Disease (PD) and Mild Cognitive Impairment (MCI). As we will see, deficits in cognitive and/or affective subcomponents of ToM might be a core feature of the early stages of such two clinical conditions, with a significant impact on quality of life and social interactions (Henry et al., 2016; Yu & Wu, 2013). Such comparison could help to clarify the specific cognitive/affective ToM profile of these two neurodegenerative disorders at early stages, according to the different pathological process involved in these two conditions.

Parkinson's Disease

A partial dissociation between cognitive and affective subcomponents of ToM has been observed in PD (for a review, see Poletti et al., 2012, and Bora et al., 2015), a neurodegenerative condition clinically defined by prominent motor symptoms (bradykinesia, rigidity, resting tremor and postural instability), often combined with non-motor symptoms, such as cognitive impairment and behavioral disturbances. In this condition, the pattern of ToM impairment has been fully characterized according to its neuropathology. In fact, the current model of ToM processing in PD linked the cognitive and affective subcomponents of ToM to different frontostriatal circuitries, which are affected in people with PD in relation to the stage of the disease (Bodden et al., 2010). In particular, the orbitofrontal frontostriatal (OFS) circuitry is associated with the affective subcomponent of ToM, while the dorsolateral frontostriatal (DLFS) circuitry is related to the cognitive ones. The neuropathological process affects, at the early stage, the dorsolateral portion of the head of the caudate nucleus, which is involved in the dorsolateral frontostriatal (DLFS) circuitry and associated with the cognitive dimension of ToM. With the progression of the disease, the prefrontal cortex and the orbitofrontal frontostriatal (OFS) circuitry are progressively affected, resulting in a deficit of affective ToM (Bodden et al., 2010). Research on this topic confirmed this hypothesis, finding ToM difficulties primarily on the cognitive component of ToM in the early stage of the disease, while the affective component seems to be involved only in the more advanced disease's stages (for a review, see Poletti et al., 2012).

Alzheimer's Disease

Emerging evidence suggests that deficits in social cognition (including ToM) occur also in Alzheimer's Disease (AD) a neurodegenerative condition which progressively results in severe cognitive impairment and dementia. In this case, the performance of cognitive ToM tasks seems to be impaired, according to the neuropathological process of AD, which firstly affects the temporoparietal regions involved in cognitive ToM reasoning (Kemp et al., 2012; Poletti et al., 2012). In particular, AD subjects show impairments in the second order false belief tasks, while the ability to attribute beliefs remains intact in the basic-level tasks such as the first order ones (Kemp et al., 2012). However, ToM deficit in people with AD seems to be secondary to their cognitive impairment instead of a main deficit of ToM. In fact, second order tasks are more cognitively demanding compared to first order belief tasks. On the contrary, a recent study suggested that social cognitive impairment may constitute a specific constellation of AD symptoms, distinct from a more general cognitive decline (Cosentino et al., 2014). Regarding affective ToM, it has been hypothesized a possible involvement of the affective mentalizing abilities only in advanced stages of the disease, when the cortical degeneration affects also the pre-frontal regions (Kemp et al., 2012). However, only a few studies investigated affective ToM in people with AD, with conflicting results probably arising from the different tasks used (for a review, see Kemp et al., 2012).

Mild Cognitive Impairment

Changes in social cognitive functions have been outlined also in the early stage of AD dementia, such as in Mild Cognitive Impairment (MCI), a preclinical condition involving an increased risk to develop AD (Albert et al., 2011). MCI is characterized by a degree of cognitive impairment that is greater than expected according to the individual's age and education level but does not significantly interfere with the functional activities of daily life (Petersen et al., 2018). People with MCI may show slight deficits in a single cognitive domain, usually memory, or more widespread deficits affecting multiple domains (usually memory and other cognitive domains) (Petersen et al., 2018). It has been widely demonstrated that multi-domain MCI people are more likely to convert to AD and to develop behavioral disturbances and interpersonal problems commonly observed in dementia (Petersen et al., 2018). For this reason, early detection of ToM impairment can be useful to identify individuals who can benefit from early treatment of cognitive and behavioral symptoms. A recent meta-analysis (Bora et al., 2017) of social cognition in MCI demonstrated that MCI individuals significantly underperformed healthy control subjects in a variety of ToM tasks. However, no studies explored the course of affective and cognitive ToM deficits from a longitudinal perspective, which is the focus of Chapter 2 of this thesis.

This Thesis

The present dissertation focused the attention on age-related changes of cognitive and affective Theory of Mind abilities in unsuccessful neurocognitive aging, and in particular on a preclinical condition just on the threshold between healthy elderly individuals and people with dementia: the Mild Cognitive Impairment (MCI). Given the higher risk to develop dementia, MCI represent the most interesting condition to investigate: A) if ToM performance could be considered as a possible marker for the disease progression (Chapter 2 and 3); B) if ToM performance could represent a potential outcome measure of a multidimensional intervention (Chapter 3); C) if ToM tasks could constitute valid assessment tools to discriminate between successful and unsuccessful aging (Chapter 3) and between different neurodegenerative pathologies (Chapter 4). In particular:

Chapter 2 evaluate the developmental changes of ToM in people with amnestic Mild Cognitive Impairment (aMCI). For this purpose, twelve aMCI subjects have been evaluated longitudinally (at the baseline and after 6 months) with neuropsychological tests and a paper-pencil battery of ToM tasks assessing both cognitive and affective dimensions of ToM. Our results showed that while the performance to the cognitive ToM tasks decreases from the baseline to the follow-up, the opposite trend emerges as regards the affective ToM performance, highlighting a possible link between ToM and cognitive processes in aMCI subjects whose cognitive functioning tend to worse over time. These preliminary findings introduce the importance of ToM evaluation in addition to the standard neuropsychological assessment, in people at risk to develop dementia.

Chapter 3 has expanded the aim of Chapter 2 investigating, in a longitudinal perspective, potential changes of cognitive and affective ToM abilities in aMCI sample involved in a Multi-Stimulation Treatment at Home (MST@H) developed to reinforce motor, cognitive and social skills. The results suggested that both cognitive and affective dimensions of ToM can be considered as potential longitudinal predictors of the disease progression, also in relation to intervention strategies towards the conversion into frank dementia. Moreover, we demonstrated that ToM performance can constitute a valuable outcome measure of a multidimensional intervention such as MST@H, in addition to the conventional cognitive measures.

Chapter 4 investigate ToM tasks as assessment tools able to distinguish between different neurodegenerative pathologies. To this end, we investigated both cognitive and affective dimensions of ToM using for the first time the computerized Italian version of the Yoni task (Shamay-Tsoory & Aharon-Peretz, 2007), together with a ToM battery that includes both cognitive and affective ToM tasks, in two non-demented neurodegenerative pathologies: Mild Cognitive Impairment (MCI) and Parkinson's Disease (PD). Our preliminary results showed that the Yoni task is able to detect detecting different patterns of ToM impairment (cognitive vs. affective) at different levels of complexity (first- and second-order) in people with MCI and PD already at the early stages of the disease and in the absence of dementia.

Chapter 2

Theory of Mind evolution in Mild Cognitive Impairment: preliminary evidence from a longitudinal study

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Introduction

The ability to understand one's own and other's mental states and referring to them to infer other's behavior, represent the pick of human evolution from cognitive and social point of view. In the psychological field, this set of skills are known by the term "Theory of Mind" (ToM). ToM has been classically described as a multidimensional process that allow people to interpret and predict behavior on the basis of other's intentions, emotions, desires and beliefs. Its investigation have always aroused interest in the developmental and clinical psychology, since pioneering studies with chimpanzees (Premack and Woodruff, 1978).

According to neuropsychological studies which focused on neurological or psychiatric disorders affecting social behavior, such as Asperger syndrome and autism (Baron-Cohen et al., 1995, 2001), schizophrenia (Shamay-Tsoory et al., 2007) or brain damage (Shamay-Tsoory et al., 2005), it is possible to distinguish between two kind of ToM representation, *cognitive* and *affective*, in the light of their respective cognitive (thinking about belief, thoughts and intentions of others) or affective (reasoning about emotions or feelings of other people) demands (Shamay-Tsoory et al., 2007, 2010; Duval et al., 2011; Dodich et al., 2015).

In recent years, the focus of attention has shifted from childhood to the pattern of ToM changes in later lifespan development (Moran, 2013; Kemp et al., 2012, Sandoz et al., 2014). Most of the research show a progressive decline in ToM abilities with advancing age and with increasing task difficulties. For example, with regard to a classic ToM instrument as *false belief task*, generally used to assess cognitive ToM, old people show worse performance in high-level ToM tasks, such as *second order false belief*, than in more simple ones like *first order false belief* (Cavallini et al., 2013; Duval et al., 2011). Other studies confirm these results using advanced ToM task like *Strange Stories* (Happè et al., 1994), showing that older adults score significantly less than younger ones, whereas no differences in performance was usually found in control stories (Sullivan and Ruffman, 2004; Charlton et al., 2009; Duval et al., 2011). Considering a fewer investigated field such as affective components of ToM, most of the studies in the literature shows contradictory results. Some authors have demonstrated an age-related decline in the ability to infer the protagonist's mental state and feelings from several task, including the Reading the Mind in the Eyes test (RME test; Baron-Cohen et al., 2001), whereas with the same task other studies reported no differences in ToM performance in relation to ages (Castelli et al., 2010).

In recent years, brain-imaging techniques have become one of the most useful tools for exploring neural structures and functions both in normal aging and neurodegenerative diseases. More specifically, neuroimaging studies have investigated how specific behaviors and abilities, such as ToM, depend on brain structures and physiology (Schurz et al., 2014; Mahy et al., 2014; Cabinio et al., 2015). The latest investigations in age-related clinical conditions like dementia highlights specific impairment of ToM competences in relation to the progressive involvement of cortical and subcortical brain structures in different neurodegenerative pathologies (Adenzato and Poletti, 2013; Kemp et al., 2012; Poletti et al., 2012; Sandoz et al., 2014).

Alzheimer's disease (AD) is a typical clinical condition that leads to the loss of social skills, especially the more advanced levels of ToM competences, whereas the more basic aspects of social cognition are still preserved (Castelli et al., 2011; Gregory et al., 2002; Verdon et al., 2007; Zaitchik et al., 2006). A decline of ToM in people with Mild Cognitive Impairment (MCI) has also been reported (Baglio et al., 2012; Poletti and Bonuccelli, 2013). MCI represent a preclinical stage which refers to the transition from an healthy condition to early AD condition (Petersen, 2004; Petersen et al., 2009). People with MCI show mild cognitive deficit in different cognitive domain, such as memory, language skills and attention. However, their general cognitive functioning and their functional competences in daily life seem to be preserved. More severe memory problem typifies *amnestic* MCI condition (aMCI), which is a really interesting clinical conditions considering their high risk to convert to AD. The typical rates of AD conversion is nearing 14-18% per year and there is also evidence of a reversion from MCI to normal or near-normal condition ranging from 4% to 15% in clinical trials and 29% to 55% in population-based studies (Koepsell and Monsell, 2012; Sachdev et al., 2013). There are few evidence in literature about the evolution of ToM in the MCI condition. Baglio and colleagues (2012) found lower performance in *second order false belief tasks* in people with aMCI compared to healthy controls (Baglio et al., 2012), whereas no significant differences were observed in aMCI people compare to control subjects in the behavioral performances to the RME test (Castelli et al., 2010), which is one of the most used task to investigate affective ToM. However, there are no studies investigating whether and how ToM performance change across time in MCI condition. This is particularly interesting in the light of the complex development of such conditions, towards an high risk of conversion to dementia or towards the opposite direction, the normal condition.

In the direction of our previous investigations, we conduct a pilot study aimed to explore in aMCI subjects the possible connections between the performance to ToM tests and the performance to neuropsychological battery adopting a longitudinal perspective.

Materials and Methods

Participants

Twelve subjects diagnosed with aMCI according with Petersen criteria (Petersen, 2004) and Grundman operational criteria (Grundman et al., 2004) were included in the study from outpatients attending a specialist dementia clinic [mean (SD) age: 76,9 (5,96) years; range 66-86 years; female : male ratio 6 : 6; mean (SD) education: 11 (4,24) years; see Table 1 for demographic details]. In detail, to be included in this study all the aMCI participants had to meet the following inclusion criteria: memory complaint, confirmed by an informant; abnormal memory function, documented by a neuropsychological evaluation; normal general cognitive function, as determined by Clinical Dementia Rating Scale (CDR; Morris, 1993), with at least a 0.5 in the memory domain, and MMSE score (Folstein et al., 1975) greater than or equal to 24; no impairment in functional activities of daily living as determined by a clinical interview with the patient and informant; no significant cerebral vascular disease, with Hachinski score less than or equal to 4 (Rosen et al., 1980) and no white matter hyperintensities outside the normal range on the basis of patient's MRI structural scans. All subjects underwent two evaluations: at baseline and after six months. Each session included the neuropsychological assessment and the Theory of Mind assessment. The study was conformed to the ethical principles of the Helsinki Declaration and informed written consent was recollected from all subjects before starting.

	aMCI
N	12
Age (years) *[Mean±SD; range]*	76.9 ±5.96; 66-86
Level of education (years) *[Mean±SD; range]*	11 ±4.24; 5-17
Gender *(M:F)*	6:6
MMSE *[Mean±SD; range]*	27.4 ±2.06; 25-30

Table 1: Range, mean and standard deviation (SD) scores of demographic information and MMSE score at the baseline (T0).

Neuropsychological Assessment

The global cognitive level was assessed at the baseline and after 6 months, using the Mini Mental State Examination (MMSE; Folstein et al., 1975), and the Montreal Cognitive Assessment (MoCa; Conti et al., 2015). Memory was evaluated through the Free and Cued Selective Reminding test (FCSRT Delayed Free Recall (DFR) and Immediate Free Recall (IFR); Frasson et al., 2011); executive functions were tested with the Phonemic Fluencies (F.A.S.; Carlesimo et al., 1995), the Semantic Fluency (Novelli et al., 1986), and the Colored Progressive Matrices (CPM), Raven, series A-Ab-B (Carlesimo et al., 1995; Raven, 1965). All the scores obtained from each test were corrected for age and educational level (conversion formulae are reported in the references of each neuropsychological test as mentioned above).

Theory of Mind Assessment

ToM ability was assessed with a paper-pencil battery of tasks appositely devised for research on adult and older people (Castelli et al., 2010, 2011; Baglio et al., 2012). This battery investigate ToM reasoning at different levels of complexity and from both cognitive and affective point of view.

As regards cognitive ToM, three tasks were used: the *Deceptive Box Task* (Perner, Leekam and Wimmer, 1987), the *Look-Prediction* and the *Say-Prediction* tasks (Antonietti, Liverta-Sempio and Marchetti, 1999; Perner and Wimmer, 1985; Sullivan, Zaitchik and Tager-Flusberg, 1994) and a selection of stories from the *Strange Stories* task (Happè, Brownell and Winner, 1999; Happè, 1994; Italian translation by Mazzola and Camaioni, 2002).

The *Deceptive Box Task* assess the first level of false belief reasoning, with a closed box shown to each subject. The content of the box has been previously substituted without participant's knowledge. At first each subject is required to say what such closed box contains. After that, the box is opened, the real content is shown and the box is closed again. Finally, the participant is asked to predict what another person would say if showed the closed box.

The *Look-Prediction* and the *Say-Prediction* tasks assess the second level of false belief reasoning. The participant has to predict the place where a character of the story thinks that another character would look for an hidden object (Look-prediction) or what a character thinks that the other ones would say about an hidden object (Say-prediction).

The *Strange Stories* assess a more advanced level of ToM reasoning with a selection of four mentalistic stories (content refers to mental states) and four physical stories (content with no reference to mental states) as control condition.

Finally, affective ToM was assessed with the *Reading the Mind in the Eyes test* (RME test, Baron-Cohen et al., 2001). It consist of 36 pictures of the eye region from different human faces. Participants have to infer what the character is feeling of thinking and choose one from four mental states written under each picture, whereas the Gender Test was used as a control condition to test basic visual faces discrimination capacity such as gender attribution.

The whole battery was administered individually; answer were coded once the session was closed. For a more exhaustive description of the battery, please refer to Castelli et al. (2010).

Data analysis

Descriptive statistic included frequencies for categorical variables and means and standard deviation (SD) for continuous measures.

A non-parametric statistic was used to compare ToM performance at T0 with ToM performance at T1 for all the tasks showing a non-normal distribution. Subjects with no more than one mistake to control questions in the Deceptive Box Task, the Look-Prediction and the Say-Prediction tasks, and the Strange Stories were included in the analysis. As regards the Gender Test and the Physical Stories - respectively the control tasks for the RME test and the Strange Stories task - all subjects are well above the cut-off.

Furthermore, the Pearson correlation coefficient (*r*) was used to verify the intensity and the direction of the relation between ToM and neuropsychological performance at T0 and at T1.

Results

Neuropsychological assessment

Demographic and clinical characteristics at the baseline of the included subjects were presented in Table 1. Table 2 shows the results to the longitudinal neuropsychological assessment. Two subjects dropped out from the study: one moved to another location, while the other had a physical accident. At 6 months, all aMCI participants were not AD “converter” and the longitudinal neuropsychological evaluations showed no significant changes in global cognitive performance (MMSE and MoCA). No changes were found also in neuropsychological tests (see Table 2 for details).

	Cut-off	Baseline		Follow-up		Goup comparison
		Mean	SD	Mean	SD	*p*_value
Cognitive functions						
MMSE	23.80	27.97	1.94	27.97	1.01	n.s.
MoCa	17.36	21.85	4.42	21.14	3.16	n.s.
Phonological Fluencies	17.35	28.40	11.3	28.60	8.25	n.s.
Semantic Fluences	25	35.20	7.48	34.50	9.51	n.s.
FCSRT - IFR	19.60	23.89	5.23	22.69	6.66	n.s.
FCSRT - DFR	6.32	7.15	3.71	6.06	4.76	n.s.
Raven CPM	18.96	29.43	4.71	27.53	5.86	n.s.

Table 2: Mean and Standard Deviation (SD) scores of Neuropsychological tests at the baseline and at the follow-up (6 months later) in aMCI patients (n = 10); n.s.= not statistically significant ($p \geq 0.05$).

ToM assessment

Table 3 shows the results of ToM assessment. No significant differences were found at follow-up compared to the baseline evaluation in the Deceptive Box task, the Look Prediction task, the Say prediction task, and the Strange Stories task. However, it may be worth noticing that the performance to the ToM tasks become slightly worse over time, even if the differences between the two ToM evaluations were not statistically significant yet. The only task that showed an improvement between T0 and T1 close to significance (p = 0.058) is the RME test, a task that evaluates affective components of ToM.

Finally, Pearson's correlations between neuropsychological tests and ToM tasks revealed a statistical significant correlation between the $FCSRT_{DFR}$ and the performance to the second order false belief tasks (r = 0.671; p = 0.0335) at baseline and between the $FCSRT_{DFR}$ and the performance to the RME test (r = -0.670; p = 0.0341) after 6 months.

	Range	Baseline		Follow-up (6 months)		Goup comparison
		Mean	SD	Mean	SD	p_value
ToM tasks						
Deceptive Box	0-5	5.00	0.00	5.00	0.00	n.s.
Look Prediction	0-5	4.30	1.10	4.10	0.99	n.s.
Say Prediction	0-5	3.80	1.20	3.70	1.25	n.s.
Strange Stories	0-8	4.90	1.45	4.50	2.01	n.s.
Physical Stories	0-8	7.00	1.50	6.50	1.08	n.s.
RME test	0-36	18.70	6.13	21.10	5.88	n.s. (p=0.058)
Gender Test	0-36	33.00	3.20	32.40	4.06	n.s.

Table 3: Mean and Standard Deviation (SD) scores of ToM tasks at the baseline and at the follow-up (6 months later) in aMCI patients (n = 10)

Discussion

In the scientific debate concerning the evolution from successful to unsuccessful neurocognitive aging (Reuter Lorenz, 2002; Reuter Lorenz & Lusting, 2005), the present work constitutes an attempt of evaluating the developmental changes of ToM in aMCI patients, the most vulnerable clinical population at risk of developing AD condition. The present aMCI sample showed a stable neuropsychological and ToM profile at the follow-up evaluation, with no AD conversion. Certainly, these results may be due to the short follow-up period but they could be also related with the amount of educational level of the subjects. In fact, a higher education is associated with a lower risk of dementia and contribute to determine high cognitive reserve levels in conjunction with higher levels of intelligence and occupational attainment. Therefore, cognitive reserve represent an important factor that could attenuate the negative effects of cerebral ageing, acting as a protection factor for dementia (Stern, 2002, 2009).

Interestingly, in our study some differences emerged when cognitive and affective demands are considered with regard to different evolution in ToM tasks and they can provide a contribution to the open debate about the dependence/independence of ToM from the cognitive domain. Our results indeed underlines that, despite the general maintenance of mentalistic functioning, a difference (although not significant) were observed between cognitive and affective ToM: while the performance at the Look Prediction/Say Prediction tasks, at the Deceptive Box task and at Strange Stories task decrease from the baseline to the follow-up, an opposite trend emerges as regard the RME test, which is one of the most used task to evaluate affective components of ToM. Moreover, correlation analysis seem to show that high long term memory performance are relate to high levels of complex cognitive ToM reasoning (second order false belief tasks) and resulted to be inversely correlated to the performance to an affective ToM task (the RME test) at follow-up. Taking together, this data support a possible link between ToM and cognitive processes and highlighted the importance of better defining the evolution of the relation between neurocognitive and ToM functioning in a longitudinal perspective. Such a relation cannot be given for granted, rather it is characterized by plasticity, thus evolving either in the direction of maintenance, or decay, or improvement. In a life-span perspective on development, it is quite obvious that in the first phases of the life course (infancy, childhood, and adolescence) this relation evolves in the direction of a functional and successful acquisition. This is not so obvious in a period of the life course characterized by the process of aging and in the presence of a borderline condition like the one of aMCI. Cognitive abilities supporting ToM may change in aging, allowing individuals to maintain high level of ToM performance by drawing on the preserved set of cognitive skills. The ability to choose the most useful cognitive support available accounts for the concept of mind/brain plasticity, as also demonstrated by neuropsychological studies. Castelli and colleagues (2010) found no differences between young and old participant in the performance to the RME test at a behavioral level; however, they observed a significant shifting in terms of the neural circuits involved in each group to solve the task. These different activation may account for a brain reorganization during successful aging and may represent a compensation due to neural plasticity (Castelli et al., 2010).

In conclusion, according to the DSM-V (2013) criteria that have introduced an assessment of ToM for Major Cognitive Disorders, and with the suggestions (Adenzato and Poletti, 2013) to introduce ToM task in standard neuropsychological assessment, it is important to investigate not only the cognitive evolution of the aging population, but also ToM, a key-component of social cognition that allows people to manage everyday social interactions that are relevant for the quality of life and for the well-being of the elderly.

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Chapter 3

Social Cognition in Rehabilitation Context: different evolution of Affective and Cognitive Theory of Mind in Mild Cognitive Impairment

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Abstract

Aim: Deficit of Theory of Mind (ToM), a key aspect of Social Cognition, characterize the early stage of neurodegenerative disorders, including Mild Cognitive Impairment, a pre-clinical condition at high risk to develop dementia [1]. Studies showed that multidimensional risk factor interventions are able to counteract the conversion into dementia [2]. The aim of this study was to investigate, in a longitudinal perspective, potential changes of cognitive and affective ToM abilities in a MCI sample involved in an multi-stimulation treatment at home (MST@H) developed to reinforce motor, cognitive and social skills. ***Materials and Methods:*** 30 MCI (77.00±4.60years), suitable for performing a structured six-weeks MST@H, underwent three steps of evaluation (T0: baseline, T1: 6 months follow-up, T2: 12 months follow-up) with conventional neuropsychological tests and ToM tasks (Deceptive Box task; Reading the Mind in the Eyes test - RME; Strange Stories task - SS). ToM abilities at T0 were compared between MCI subjects and 21 matched healthy controls (HC; 74.95±3.88years) (t-test). Longitudinal changes (T0 *versus*T2) in ToM abilities of MCI sample were investigated (ANOVA Repeated Measure). Finally, a correlation analysis between RME and SS changes (T2 *vs*.T0) was performed in MCI group. ***Results:*** The T0 comparison showed that the MCI group underperformed the HC group in complex ToM tasks (MCI<HC*:* SS task, $p<.001$; RME test, $p=.002$). Repeated Measure ANOVA highlighted that the MST@H program had an impact both on some sub-cognitive domains of MoCA (memory: T0<T1, $p_{corr}=.019$; executive functions: T1<T2, $p_{corr}=.006$, T0<T2, $p_{corr}<.001$), and on cognitive ToM (T0<T2, *SS task* $p_{corr}=.009$), while the affective ToM remains stable over time (T0=T2, RME p_{corr} >.05). At the T2, we found a statistically significant inverse relationship between decrease in cognitive ToM task (SS) and increased RME score ($r=-.522$, $p=.009$). These changes are statistically significantly different between subjects with preserved or decreased cognitive *status*. ***Discussion and Conclusion:*** These results confirm an initial decline of high-level ToM competences in MCI when cognitive skills tend to worsen over time. Moreover, we observed a

possible role of MST@H in preventing conversion into blown dementia, perhaps strengthening the affective ToM to counteract the progression of cognitive decline while preserving social functioning.

Introduction

Social cognition refers to the psychological processes that allow individuals to make inference about other people in the context of social interaction (Adolphs, 2009). It represents a crucial competence for dealing with our interpersonal relationships in everyday life, by enabling us to anticipate and interpret other's behaviors. In recent years, there has been a substantial increase in the number of studies that investigate social cognitive functions in neurodegenerative diseases, due to a greater awareness concerning the critical role of social cognition in functional and cognitive disability (Henry et al., 2016). Recently, the American Psychiatric Association's introduced social cognition as one of the six core neurocognitive domains in the latest edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5), and upholds the importance of the clinical assessment of social cognitive function in several mental disorders, in addition to the conventional neuropsychological assessment.

One of the key component of social cognition is Theory of Mind (ToM; Premack and Woodruff, 1978), which refers to our ability to understand own and other's cognitive (thoughts, belief, and intentions: "cognitive ToM") and affective (emotions or feelings: "affective ToM") states, and to predict other's behaviors on the basis of such mental representations. It is now well documented that failures in such different dimensions of ToM function may represent a core feature of many clinical conditions, leading to impairments in social functioning and poor quality of life (for a review, see Cotter et al., 2018). A growing body of research suggests that ToM performance may be used as a screening tool for differentiating between different forms of neurodegenerative conditions (Bora et al., 2015, 2016; Bertoux & Hornberger, 2015). Moreover, the assessment of ToM competences provides the opportunity to monitor the disease progression (Cotter et al., 2018). This is particularly helpful in Alzheimer's Disease (AD), a neurodegenerative condition which represents the most common cause of dementia according to the World Health Organization (WHO). AD is actually defined as a *continuum* of pathology between elderly individuals with Mild Cognitive

Impairment (MCI), and people with frank dementia (Dubois et al., 2016). With the progressive neurodegeneration, many AD patients show impaired social functioning in addition to cognitive, functional and behavioral problems. Specifically, high-levels of cognitive ToM seem to be impaired, especially in the second level of recursive thinking, while the ability to attribute beliefs remains intact at a more basic level (first-order tasks) (for a review, see Kemp et al., 2012; Poletti et al., 2012). However, social cognitive deficits in people with AD seem to be secondary to their cognitive impairment rather than a primary involvement of ToM. In fact, second-order tasks are more cognitively demanding compared to first-order false belief tasks, where the cognitive load is minimal. This evidence suggests that ToM abilities are intrinsically related to cognitive functions. In particular, deficits in the executive functioning (shifting, inhibition, updating and planning processing) seem to contribute to ToM impairment (for a review, see Aboulafia-Brakha et al., 2011). On the other hand, only a few studies investigated affective ToM in people with AD, with inconsistent findings probably arising from the different instruments employed (Laisney et al., 2013; Poletti and Bonucelli, 2013).

The importance of the cognitive decline for ToM abilities is still an open matter of debate and the association between ToM and cognitive functioning has yet to be deeply explored in AD *continuum* also in a longitudinal perspective. Only a pilot case-report study investigated the relationship between ToM performance and cognitive *status* in a cognitive-converter MCI individual, showing a decline in the most complex levels of ToM reasoning, in particular in the Strange Stories task (Castelli et al. 2016).

In order to test the contribution of cognitive processes to the ToM performance, we adopted a longitudinal design in which MCI subjects were evaluated over time in affective and cognitive ToM components. We expected to find that cognitive and affective ToM dimensions in MCI subjects change over time in parallel with the cognitive *status*. In order to modify the cognitive *status* we studied a MCI population involved in a Multi-Stimulation Treatment at Home (the MST@H) program able to counteract the progression of cognitive decline while preserving cognitive and social functioning in daily-life (Baglio et al., 2014; Petersen et al., 2018; Lindquist, 2016).

Materials and Methods

Participants

Thirty outpatients diagnosed with aMCI were consecutively recruited from the Memory Clinic of IRCCS Don C. Gnocchi Foundation (see Table 1 for demographic details). All participants had to meet the following inclusion criteria: 1) diagnosis of MCI due to AD, according to the recommendations of the National Institute on Aging (Albert et al., 2011) and the DSM 5 diagnostic criteria (American Psychiatric Association - APA 2013); 2) age over 65 years and school attendance ≥5 years. 3) normal general cognitive function, as determined by the Mini Mental State Examination score (MMSE score ≥ 24; Folstein et al., 1975), corrected for age and years of education according to Italian normative data (Measso et al., 1993); 4) abnormal memory function confirmed by an informant and documented by three consecutive steps of neuropsychological examination; 5) no impairment in functional activities of daily living as determined by a clinical interview with both the patient and the caregiver; 6) willingness to participate in the MST@H as post-diagnostic care program for aMCI outpatients; 7) absence of psychiatric illnesses, with particular attention to exclusion of participants with a history of depression (Hamilton Depression Rating Scale score ≤ 12; Hamilton, 1960) and severe behavioral disturbance; 8) absence of severe auditory/visual loss.

Twenty-one healthy controls (HC), who were matched for age, education, and gender to the aMCI subjects (see Table 1 for demographic details), were also included in the study for the baseline comparisons, in order to determine the starting level of aMCI subjects with respect to ToM performance. They were screened according to their clinical history in order to exclude major systemic, psychiatric or neurological illnesses. In particular, the exclusion criteria for HC participants were: 1) the presence of visual or auditory deficits; 2) a positive history of psychiatric disorders or behavioral problems; 3) the presence of neurological conditions, cardiovascular diseases or cerebrovascular diseases; 4) a MMSE (Mini Mental State Examination; Folstein, et al., 1975) score ≥26.00, in order to exclude participants with dementia.

The study conforms to the ethical principles of the Helsinki Declaration (1975, revised in 2008), with the approval from the local ethics committee (Don Carlo Gnocchi Foundation, Milan). Informed written consent was obtained from all participants before the study began.

Procedure

After being consecutively recruited, all aMCI subjects underwent three steps of evaluation, six months apart (T0; T1; T2). In the first step of evaluation (*First step of evaluation*, T0), they were subjected to a conventional neuropsychological and ToM assessment to obtain their global cognitive level and to evaluate their affective and cognitive ToM profile at the baseline. Subsequently, they were tested 6 months (*Second step of evaluation*; T1) and 12 months (*Third step of evaluation*; T2) after the baseline. Between the *First* and the *Second* steps of evaluation, the aMCI participants underwent a 6-weeks MST@H following the "Multidimensional Stimulation Therapy" (MST) model proposed by Baglio et al. (2014).

First step of evaluation: neuropsychological and ToM measures

All aMCI and HC subjects were evaluated and compared at the baseline with a conventional neuropsychological and ToM battery administered by a trained neuropsychologist blinded towards the multidimensional intervention.

Among the neuropsychological measures, the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was administered to assess the global cognitive level through several subtasks: memory (M), visuo-spatial abilities (VSP), executive functions (EF), attention (ATT), language (L), and temporal/spatial orientation (OR). Adjusted and equivalent scores for the total MoCA score and for each cognitive domain sub-scores were provided according to the normative data in the Italian population sample (Santangelo et al., 2015). One of the three available parallel forms of this test (Conti et al., 2015) was used in order to avoid learning effects in the following steps of evaluation.

ToM ability was investigated at different levels of complexity and from both cognitive and affective point of view with a selection of tasks traditionally applied in research on adult and elderly subjects. The battery includes:

- the *Deceptive Box Task*, DB: Perner, Leekam, & Wimmer, 1987), which was administered as a baseline measure of ToM competences. In this first-order false belief task, participants are shown a closed box of sweets which actually contains staples rather than candies. Subjects are asked what the closed box contains before showing the real content. Then, the box is closed again, and the participants are asked what another person, who has not seen inside the closed box, will think is inside (first-order false belief question). Participants are also asked to say what they have thought about the content before opening the box (first-order own false belief question). Two control questions are also provided. Each question is scored 1 if the answer is correct and 0 if the answer is wrong (range 0-5).
- the *Reading the Mind in the Eyes test* (RME test, Baron-Cohen et al., 2001), conceived by Baron-Choen et al. (1997) to assess the attribution of affective mental states. It consists of 36 black-and-white photographs showing the eye region of different human faces, either male or female. Participants have to choose which word best describes what the person is thinking or feeling from four mental states terms written under each picture. A glossary for each term was available to participants in order to minimize comprehension difficulties and an example was provided at the beginning of the task to familiarize subjects with the material. The Gender Test was used as a control condition assessing a basic visual face

discrimination ability such as gender attribution. Each item is scored 1 if the answer is correct and 0 if the answer is wrong (range 0-36);

- A selection of four stories from the *Strange Stories* task (SS task; Happè, 1994) to assess a more advanced level of ToM reasoning about the social world, which could be considered mainly a cognitive ToM task. In the Strange Stories task, four mentalistic stories were read to the participants consequently. At the end of each story, participants asked three questions: the comprehension question, the mentalistic question and the justification one. Four physical stories were also used as a control condition, in order to assess the understanding of physical events and check the presence of any comprehension deficit. The physical control stories had just one question. Each question received a score of 0 for wrong answers, 1 for partially correct/incomplete answers and 2 for correct answers (range 0-2 for each question). The global scores of the four "ToM stories" and of the four physical stories ranged from 0 to 8.

Subjects with no more than one mistake to control questions in the SS task were included in the analysis. The performance of the control tasks (the Gender test for the RME test and the physical stories for the SS task) was also considered.

Second step of evaluation

The aMCI group performed the second step of evaluation after 6 months from the baseline (T1) using a parallel form of the MoCA test, in order to avoid learning effects (Conti et al., 2015). Between the T0 and the T1, all aMCI participants took part in MST@H. Such intervention consists of 30 home-based rehabilitation sessions over 6 weeks according to the "Multidimensional Stimulation Therapy" (MST) model proposed by Baglio and colleagues (2015). The training involves daily cognitive activities (5 days a week), light aerobic physical activities (7 days a week) and occupational/recreational activities aimed to promote the patient-caregiver interaction at home (7 days a week). The paper-pencil cognitive activities were designed to reinforce multiple cognitive domains, such as memory, attention, executive functions, language and visuo-spatial abilities. The motor activity consisted of a 30-minute walk, once a day, to be carried out at any time of the day. Before starting the program, the researcher provided participants and their caregiver with a brief training session including instructions on the number of days per week in which to perform the cognitive and motor exercises. Phone contacts from the care manager were also planned during the six weeks of intervention to support the patient-caregiver dyad and to verify the adherence to the training program.

Third step of evaluation

In the third step of evaluation 12 months after the baseline (T2), the aMCI subjects underwent both the neuropsychological assessment, using a parallel form of the MoCA test (Conti et al., 2015), and the ToM evaluation, with the same battery proposed in the T0. The rate of clinical conversion from MCI to AD was also collected at T2 evaluation.

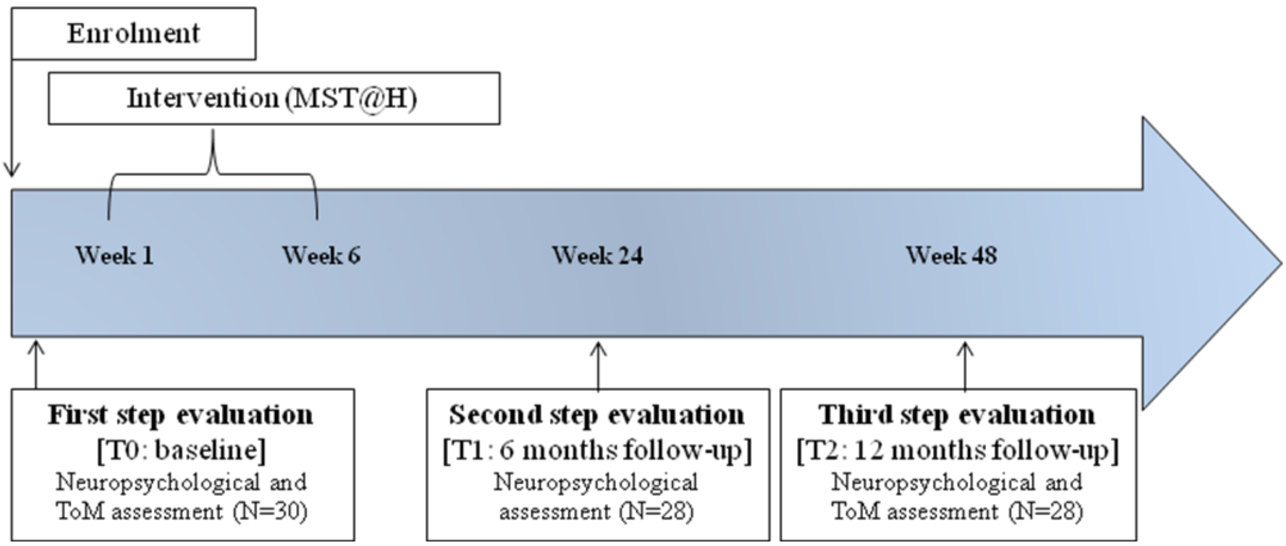

Figure 1: Timeline of the longitudinal study. MST@H=Multi-Stimulation Treatment at Home program.

Data analysis

All statistical analyses were conducted using the IBM SPSS Statistics software, version 24. Descriptive statistic included frequencies for categorical variables and Means and Standard Deviation (SD) for continuous measures.

To test the level of cognitive and affective ToM competences in people with aMCI, compared at the T0 with a group of HC, we used independent two-sample t-test (two-tailed with *p*-value < 0.05 was considered statistically significant).

In order to monitor ToM abilities over time, a Repeated Measure ANOVA was performed within the aMCI group. The within-subjects factors were summarized with Mean and Standard Deviation. In the Pairwise comparisons, the different measurements were compared to each other and LSD *Post-hoc* correction for multiple comparisons was applied for *p*-values. Results have been considered as statistically significant when surviving *p corrected* <0.05 threshold.

Then, a partial correlation analysis (with age and educational level considered as nuisance covariates) was conducted in aMCI group in order to test the relationship between RME changes (T2 Vs. T0) and SS changes (T2 Vs. T0).

Finally, according to the differences between the T2 and the T0 (T2 Vs. T0) on the MoCA test (conventional clinical measure of disease progression on cognitive domain), the aMCI group has been split into two sub-groups: the MoCA+ (MoCA T2 Vs. T0 ≥ 0) subjects, and the MoCA- (MoCA T2 Vs. T0 < 0) subjects. An independent two-sample *t*-test was computed between these two groups (MoCA+; MoCA-) on changes (T2 Vs. T0) in neuropsychological tests and ToM tasks. A statistical threshold of *p*<0.05 was considered statistically significant.

Results

Neuropsychological and ToM assessment at Baseline: comparison between MCI and HC groups

Table 1 reports the demographic and clinical characteristics of the sample. aMCI and HC subjects showed similar demographic characteristics with no significant differences in age (t=1.67, *p*=0.102), educational level (t=-0.776, *p*=0.442) and sex (X^2=.25, p=.62). The global cognitive level (MMSE score) was significantly poorer in the aMCI group compared to the HC group (t=-4.717, *p*<0.001).

Table 2 reports the scores (Mean±SD) of the neurpsychological assessment (the MoCA test with its specific cognitive domains sub-scores) and ToM tasks (the DB task, the SS task, and the RME test) for each group. The comparison between the aMCI group and the HC group showed a significant difference in the total score of the MoCA test (t= -9.69, *p*<.001), and in VSP (t= -4.94, *p*<.001), EF (t= -5.83, *p*<.001), M (t= -6.11, *p*<.001), L (t= -4.26, *p*<0.001), and OR (t= -2.81, *p*<.05) sub-scores, but not in ATT sub-score (t=-1.65, *p*>.05).

As regards the ToM tasks, no differences emerged for the first-order ToM task (the DB task), which showed a ceiling effect. Regarding the advanced ToM tasks, all subjects exhibited good performance on the control tasks (the Gender test and the physical stories), while significant between-group differences emerged on the RME test (t= -3.42, *p*<.005) and the SS task (t= -4.25, *p*<.001), with lower scores of the aMCI group compared to the HC group.

	aMCI	HC	**Group Comparison** *p value* (*)
N (subjects)	30	21	
Age (years; *mean±SD*)	77.00±4.60	74.95±3.88	0.102
Education (years; *mean±SD*)	10.30±3.53	11.10±3.70	0.442
Sex (M:F)	15 : 15	10:12	0.615
MMSE (total score; *mean±SD*)	27.45±1.91	29.60±0.97	**<0.001**

Table 1: Clinical characteristics of sample at baseline evaluation (T0).

(*) Independent two-sample *t*-test (in bold the statistical significant values, *p*<0.05). aMCI= amnestic Mild Cognitive Impairment; HC= Healthy Controls; N=Number; SD= Standard Deviation; M=Males; F=Females.

Longitudinal ToM evalutation

Table 3 illustrates the descriptive data and the comparisons between each step of evaluation (T0; T1; T2) of the longitudinal analysis within the aMCI group (Repeated Measure ANOVA). At the T2, three participants out of 30 were excluded from the analyses: two subjects drop out from the study and one subject converted into frank dementia.

The Repeated Measure ANOVA showed that some within-subject factors change over time. Specifically, significant differences emerged in the total score of the MoCA test (F=4.776 (2), η^2= .155, ω= .771, p<.05), with a better performance in T1 and in T2 compared to T0 (T0<T1, p<.05; T0<T2, p<.05), and in some cognitive sub-domains: EF (F=9.782 (2), η^2=.273, ω=.977, p<.001), M (F=3.207 (2), η^2=.110, ω=.588, p<.05) and OR (F=3.927 (1.63), η^2=.131, ω=.616, p<.05). In particular, pairwise comparisons showed an improvement of the executive function (T1<T2, p<.05; T0<T2, p<.001), and memory (T0<T1, p<.05), while orientation gets slightly worse (T1>T2, p<.05; T0>T2, p<.05) (Table 3).

As concerns the first level of ToM reasoning, our results showed that the first-order ToM task (the DB task) remains stable over time. Regarding the advanced ToM tasks, our results showed a significant improvement in the SS task (T0<T2, F=7.947 (1), η^2=.234, ω=.774, p<.05), while the RME test remains stable over time (F=0.117 (1), p>.05) (Table 3).

	aMCI [N=30]	HC [N=21]	Group Comparison
	mean±SD	*mean±SD*	*p value (*)*
MoCA test			
TOT	21.31±2.36	27.93±2.46	**<0.001**
VSP	2.93±1.02	4.10±0.44	**<0.001**
EF	2.33±1.17	3.95±0.60	**<0.001**
M	0.53±1.20	2.90±1.58	**<0.001**
ATT	5.69±0.83	6.07±0.74	0.105
L	4.80±1.01	5.83±0.53	**<0.001**
O	5.50±0.83	6.02±0.21	**0.002**
ToM tasks			
DB task	5.00±0.00	5.00±0.00	1.000
SS task	4.17±1.90	6.24±1.41	**<0.001**
RME test	18.27±6.17	23.81±4.94	**0.001**

Table 2: Neuropsychological and ToM results at baseline evaluation (T0).

(*) Independent two-sample *t*-test (in bold the statistical significant values, $p<0.05$). aMCI= amnestic Mild Cognitive Impairment; HC= Healthy Controls; N=Number; SD= Standard Deviation; MoCA= Montreal Cognitive Assessment test; TOT= MoCA total score; VSP= Visuo-spatial abilities; EF= Executive Functions; M= Memory; ATT= Attention; L=Language; O= Orientation; ToM=Theory of Mind; DB= Deceptive Box task; SS= Strange Stories task; RME= Reading the Mind in the Eyes test.

Relationship between longitudinal changes in ToM performance and cognitive status

The correlation analysis between changes of affective measure of ToM (RME test) and of cognitive measure (SS task) showed statistically significant negative correlation (r= -.522, p=.009) between SS and RME delta score (T2 *versus* T0) (Figure 1). According to conventional primary cognitive outcome measure of treatment efficacy, the aMCI sample has been divided into the MoCA+ group (MoCA delta score T2 *versus* T0 $\geq$ 0), and the MoCA- group (MoCA delta score T2 *versus* T0< 0). The resulted two groups were comparable for age (t=.915, p=.368), sex (X^2=.039, p=.843), and global cognitive level (MMSE: t=.761, p=.453) at baseline evaluation. Table 4 highlighted a significant difference between the changes in SS task (MoCA + > MoCA -; t= 3.25, p=.003) and in the RME test (MoCA + < MoCA-; t= -2.50, p=.019) between these two groups. The opposite behavior observed in the MoCA- group was pointed out also in Figure 1 (red squares).

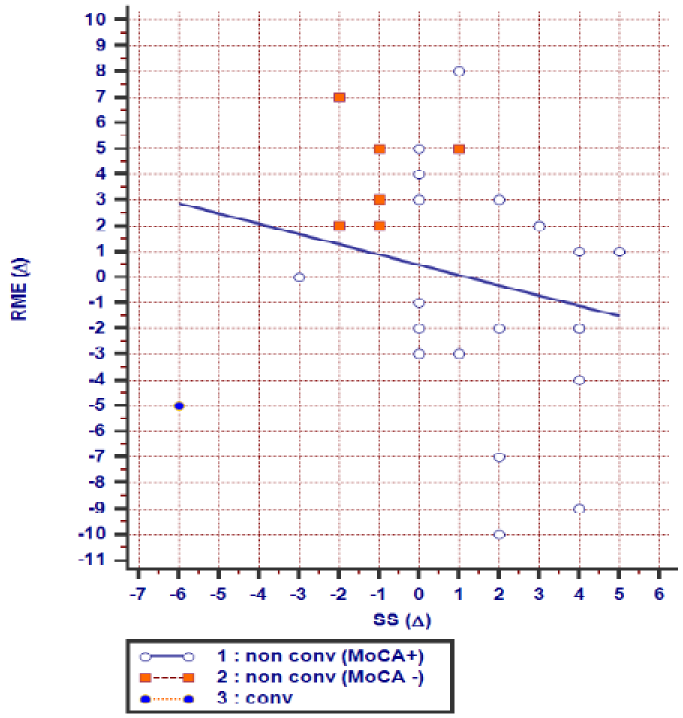

Figure 1: Correlation analysis between changes (delta score T2 Vs. T0) of RME test and SS task in aMCI sample. Non conv = non converter; Conv = converter; MoCA + = MoCA delta score T2 Vs. T0 $\geq$ 0; MoCA- = MoCA delta score T2 Vs. T0< 0.

	Evaluation (Time interval)				
	T0	**T1**	**T2**	**Time Comparison**	**Pairwise comparisons**
	mean ± SD	*mean ± SD*	*mean ± SD*	*p value(*)*	*p value(#)*
aMCI NC [N=27]					
MoCA test					
TOT	21.61±2.11	22.86±3.12	22.97±3.50	**0.012**	**T0<T1**; T1=T2; **T0<T2**
VSP	2.98±1.04	3.26±1.05	3.30±1.18	0.318	T0=T1=T2
EF	2.41±1.16	2.82±1.03	3.27±0.89	**<0.001**	**T0<T1**; **T1<T2**; **T0<T2**
M	0.57±1.23	1.21±1.55	1.04±1.51	**0.049**	**T0<T1**; T1=T2; T0=T2
ATT	5.67±0.84	5.61±0.86	5.77±0.93	0.608	T0=T1=T2
L	4.85±1.03	4.74±1.19	4.84±0.93	0.876	T0=T1=T2
O	5.64±0.65	5.57±0.88	5.21±1.35	**0.035**	T0=T1; **T1>T2**; **T0>T2**
ToM tasks					
SS task	4.11±1.93	--	5.33±1.80	**0.009**	**T0<T2**
RME test	18.29±6.39	--	18.63±5.29	0.735	T0=T2
aMCI C [N=1]					
MoCA test					
TOT	18.53	11.53	7.53		
ToM tasks					
SS task	6	--	0		
RME test	18	--	13		

Table 3: Neuropsychological and ToM results within the aMCI group at each step of evaluation (T0: baseline; T1: 6 months evaluation ; T2: 12 months follow-up).

(*) Repeated Measure ANOVA (in bold the statistical significant values, $p<0.05$; details are showed in the main text); (#) Pairwise comparisons with LSD *Post-hoc* correction (in bold the statistical significant values, p corrected <0.05); aMCI= amnestic Mild Cognitive Impairment; N= number of subjects included in the analyses; SD= Standard Deviation; MoCA= Montreal Cognitive Assessment test; TOT= MoCA total score; VSP= Visuo-spatial abilities; EF= Executive Functions; M= Memory; ATT= Attention; L=Language; O= Orientation; ToM=Theory of Mind; DB= Deceptive Box task; SS= Strange Stories task; RME= Reading the Mind in the Eyes test.

	GROUP		
	MoCA+ [N=21] *mean ± SD*	**MoCA-** [N=6)] *mean ± SD*	***Group comparison*** *p_value (*)*
MoCA *(delta score)*			
TOT	2.33±1.83	-2.50±1.64	**<0.001**
VSP	0.43±1.12	-0.17±1.17	0.266
EF	1.00±1.14	0.33±0.82	0.196
M	0.71±1.27	-0.50±0.84	**0.038**
ATT	0.29±0.85	-0.50±1.22	0.081
L	0.00±1.04	-0.17±1.72	0.769
OR	-0.19±0.81	-1.33±1.37	**0.015**
ToM tasks *(delta score)*			
SS task	1.81±2.02	-1.00±1.10	**0.003**
RME test	-0.76±4.48	4.00±2.00	**0.019**

Table 4: Results of group comparison on longitudinal changes at 12 months (T2 evaluation *versus* baseline evaluation, T0) on cognitive and ToM measure.

(*) Independent two-sample *t*-test (in bold the statistical significant values, $p<0.05$). MoCA+ = MoCA T2 Vs. T0 ≥ 0; MoCA- = MoCA T2 Vs. T0 < 0; N=Number; SD= Standard Deviation; MoCA= Montreal Cognitive Assessment test; TOT= MoCA total score; VSP= Visuo-spatial abilities; EF= Executive Functions; M= Memory; ATT= Attention; L=Language; O= Orientation; ToM=Theory of Mind; DB= Deceptive Box task; SS= Strange Stories task; RME= Reading the Mind in the Eyes test.

Discussion

In this study, we investigated ToM competences in AD *continuum* in a longitudinal perspective. Given the complex, multidimensional nature of ToM, and the age-related difficulties on ToM abilities previously detected in this population (Bora et al., 2017; Poletti et al., 2012; Sandoz et al., 2014), we focused the attention on different levels of mentalizing reasoning (the high-level ToM competences *versus* the more basic level ToM abilities), and on both cognitive and affective dimensions of ToM. Taken together, our findings highlighted the importance of the clinical assessment of ToM competences in MCI condition with different perspectives.

First of all, ToM tasks can be useful screening tools to distinguish between people in the early stages of (or at risk to develop) dementia from healthy elderly. In particular, as expected, we found that only the advanced ToM tasks are able to discriminate between aMCI and HC subjects (Duval et al., 2011; Kemp et al., 2012; Bora et al., 2017) and that such difference concern both cognitive and affective dimensions of ToM.

In this study, it should be noted that the ability to infer the mental states from the eye gaze was still quite preserved in our aMCI sample. In fact, despite an initial difficulty revealed from the comparison with the HC subjects in this ability, the RME scores in people with aMCI were still above the cut-off. On the other hand, aMCI subjects showed an impairment in the SS performance. This result could be interpreted in the light of cognitive load implicated in this complex, high-order cognitive task, which requires relatively undamaged cognitive functions.

Our second main result corroborated this assumption since we found that the cognitive ToM changes (Δ score) were in a relationship with the longitudinal, treatment-induced cognitive modifications in aMCI subjects. Consistent with studies in rehabilitation contexts which demonstrated the efficacy of multi-component interventions for dementia patients on a range of outcomes, including cognition (Olazarán et al., 2010; Kivipelto et al., 2013), in the present study the MST@H had a short-term impact on memory, which improved at the first step of evaluation and then tends to decrease over time, and a long-term effects on executive functions, since the observed improvement was preserved at the T2 follow-up.

Interestingly, we found that the SS performance increase over time in our aMCI sample, in relation to the enhancing of the remaining resources of aMCI individuals such as executive functions. The relationship between cognitive ToM and executive functioning has been previously described (Aboulafia-Brakha et al., 201; Sandoz et al., 2014) but no studies investigated such relationship in a longitudinal perspective.

The significant difference emerged between the MoCA+ and the MoCA- subjects in the SS scores further support this finding, since the individuals who improve their cognitive *status* (the MoCA+ subjects) showed a related increase in their cognitive ToM performance.

Noteworthy, our third result highlighted a significant, inverse correlation between the SS task and the RME test and a significant difference between the MoCA+ and the MoCA- groups on the RME changes (T0 *versus* T2). Interestingly, the individuals whose general cognitive functioning got worse over time (the MoCA- subjects) but not convert into frank dementia, were the same one who improved in the RME test. This results could be explained as an unexpected effect of the MST@H, which enhance affective ToM acting on the remaining resources such as language skills to preserve social functioning in daily life. It has been demonstrated that the RME performance is partially influenced by language skills, probably as a consequence of the verbal components of this test, but not by executive functions (Peterson and Miller, 2012). In our study, the language skills remain stable in people with aMCI, maybe contributing to keeping the RME performance unchanged over time. This hypothesis is corroborated by our previous work on mind-reading abilities (evaluated with the RME test) and structural connectivity changes in healthy aging (Cabinio et al., 2015), which demonstrated that the volume reduction at the level of premotor cortex, inferior frontal gyrus, insula and superior temporal gyrus, associated with a decrease of frontal and temporal connections, might result in difficulties to infer other’s mental states through the eye gaze. However, the recruitment of additional neural circuits, such as bilateral language areas, might help to preserve the RME performance (Cabinio et al., 2015; Castelli et al., 2010) in elderly subjects.

To further support the role of affective ToM as a compensatory pathway to counteract the decline in frank dementia, we can consider the behavior of the MCI-converter subject, who didn't respond to treatment and at 12-month follow-up showed abnormal performance in cognitive functioning – all domains - , and both cognitive and affective ToM. Future studies should investigate if changes in cognitive and/or affective dimensions of ToM in relation to a multidimensional intervention such as MST@H is associated with changes in the neural network involved in social cognitive processes. it should be interesting to investigate if interventions specifically designed to enhance affective ToM can help in maintaining the autonomy in daily life also acting on the remaining resources of aMCI individuals. In fact, there is preliminary evidence that socio-cognitive skills are sensitive to interventions specifically developed to promote ToM performance in healthy older adults (Cavallini et al., 2015; Lecce et al., 2015).

Further studies in rehabilitation contexts involving wider samples and comparing different type of interventions will be useful to better characterize the evolution of cognitive and affective ToM over time.

In conclusion, our longitudinal results suggested that both cognitive and affective dimensions of ToM can be considered potential longitudinal predictors of the disease progression, also in relation to intervention strategies. This illustrates the crucial importance of the clinical assessment of social cognitive function in mental disorders, as strongly recommended by the American Psychiatric Association in the latest edition of the DSM-5. Furthermore, our findings demonstrated that ToM performance can constitute a valuable outcome measure of a multidimensional intervention such as MST@H, in addition to the conventional cognitive measures, which are still overly considered at the expense of interpersonal aspects, in which ToM abilities play a crucial role.

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Chapter 4

Cognitive and Affective Theory of Mind in Mild Cognitive Impairment and Parkinson's Disease: Preliminary Evidence from the Italian Version of the Yoni Task

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Abstract

The aim of the study was to explore cognitive and affective dimensions of ToM using the computerized Yoni task in participants with Mild Cognitive Impairment (MCI=16), early stage of Parkinson's Disease (PD=14), and healthy controls (HC=18). Results demonstrated that the Yoni task was effective in discriminating between groups in 1th order cognitive dimension (MCI<PD=HC, p_{corr}<.05), and in 2nd order cognitive and affective dimensions (MCI<HC, p_{corr} <.05), highlighting an initial ToM impairment also in people with PD (MCI<PD<HC, p_{corr} <.05). Thus, the Yoni task represents a sensitive tool for detecting different dimensions of ToM impairment, across different clinical conditions

Introduction

Theory of mind (ToM) is a widely investigated construct in neuropsychology as well as in developmental and clinical psychology. It was originally described by Premack and Woodruff (1978) as the ability to infer and to represent the mental states of self and others (intentions, emotions, desires, and beliefs) and to understand and predict one's own and other people's behaviour on the basis of such mental representations. The increasing number of studies in this field have highlighted that ToM may be considered a complex, multidimensional psychological construct requiring the integration of several components, such as the attribution of intentions vs. emotions and the level of complexity of such inferences (first- and second-order level of attribution). Brothers and Ring (1992) distinguished between "cold" and "hot" aspects of ToM, later termed "cognitive" and "affective" ToM, respectively (Wang & Su, 2013). Cognitive ToM concerns the ability to understand the intentions, beliefs, and thoughts of the self and others. It can be evaluated through several tasks, such as the conventional first-order (Baron-Cohen, Leslie, & Frith, 1985; Wimmer & Perner, 1983), and second-order (Baron-Cohen, 1989; Perner & Wimmer, 1985) False Belief tasks, the cognitive subcomponent of the Faux Pas Recognition test (Stone, Baron-Cohen, & Knight, 1998) and the Strange Stories task (Happè, 1994). On the other hand, affective ToM concerns reasoning about the affective states, emotions or feelings of self and others. It is traditionally assessed using the Reading the Mind in the Eyes test (Baron-Cohen et al., 2001) and the affective subcomponent of the Faux Pas Recognition test (Stone, Baron-Cohen, & Knight, 1998).

A different paradigm introduced by Shamay-Tsoory and Aharon-Peretz (2007) systematically examined the dissociation between the cognitive and affective components of this construct at different inferential levels. The Yoni task is designed as a computerized task that evaluates the ability to judge first- and second-order affective versus cognitive mental state attributions based on simple verbal instructions and eye-gaze cues involving minimal language and executive demands

(Shamay-Tsoory & Aharon-Peretz, 2007). The Yoni task was first used to investigate cognitive and affective dimensions of ToM in patients with localized brain lesions (Shamay-Tsoory & Aharon-Peretz, 2007), people with schizophrenia (Shamay-Tsoory, Aharon-Peretz, & Levkovitz, 2007), and criminal offenders (Shamay-Tsoory et al., 2010). These studies have produced evidence of a partial dissociation between affective and cognitive ToM based on partially distinct anatomical substrates. Specifically, the Ventromedial Prefrontal Cortex (vmPFC) (Sebastian et al., 2011; Shamay-Tsoory et al., 2005), the Amygdala (Völlm et al., 2006), the Inferior Frontal Gyrus (IFG) (Bodden et al., 2013; Dal Monte et al., 2014), and the Anterior Cingulate Cortex (ACC) (Bodden et al., 2013) have been found to be important for affective ToM, whereas the Dorsolateral Prefrontal Cortex (DLPFC) (Kalbe et al., 2010; Xi et al., 2011) and the posterior temporo-parietal regions (Corradi-Dell'Acqua, Hofstetter, & Vuilleumier, 2014; Van Overwalle & Baetens, 2009) have been found to play a key role in cognitive ToM tasks.

Given the distinction between cognitive and affective ToM and the involvement of specific brain areas underlying such different facets of mentalizing, we can assume the existence of different patterns of ToM impairment according to the specific neurodegenerative condition. In particular, the extent of ToM deficits may depend on various elements, such as the topographical distribution of the brain damage and the different stages of the disease. For example, the partial dissociation between cognitive and affective subcomponents of ToM was observed in Alzheimer's Disease (AD), a neurodegenerative condition which progressively leads to severe cognitive impairment and dementia. In this case, the neuropathological process affects, in the early clinical stage, the temporo-parietal regions involved in cognitive ToM reasoning. With the progression of the disease, the cortical degeneration involves also the pre-frontal regions, with the engagement of the affective component of ToM (Kemp et al., 2012). However, concerning the latter dimension, the results appear controversial. While the majority of the studies highlight a significant impairment in the cognitive dimension of ToM, in particular in those tasks with a high cognitive load such as second-order false belief tasks, it has also been suggested that patients with AD show impaired affective ToM.

Notably, only a few studies have investigated ToM in people in a pre-dementia stage, i.e., in people with Mild Cognitive Impairment (MCI), who are at increased risk for developing AD. In fact, MCI represents a prodromal clinical phase which refers to the transition from a healthy condition to an early AD condition (Petersen, 2004; Petersen et al., 2009). People with MCI show mild cognitive deficits in a single cognitive domain (usually memory) or even in multiple cognitive domains. However, their general cognitive functioning and their autonomy in daily life seem to be preserved. Studies by Baglio et al. (2012), Moreau et al. (2015), and Poletti and Bonuccelli (2013) reported a decline of both cognitive and affective ToM in people with MCI, while Dodich et al. (2016) did not find any ToM impairment in these patients. Collectively, these findings suggest that ToM impairment may arise early in people with MCI, but the results are quite controversial given the high variability of the tasks used to evaluate ToM. Therefore, further research is needed to better define the specific pattern of ToM difficulties in this clinical population, and to examine its possible relationship with deficits in cognitive functions.

A possible way to reach this goal would be to compare the ToM functioning of individuals diagnosed with MCI, predominantly typified by cognitive symptoms but in absence of dementia, to that of individuals with a neurodegenerative disease characterized mainly by motor symptoms and in the absence of severe cognitive impairment, such as the early stage of Parkinson's Disease (PD). It has been demonstrated that people with Parkinson's Disease (PD) show cognitive ToM deficits, in both the early and moderate stage of the disease. On the contrary, affective ToM seems to be preserved at the very early stage of the disease – less than five years of disease duration (Poletti et al., 2012; Bora et al., 2015). According to the current model of ToM processing in PD, cognitive and affective subcomponents of ToM may be associated to different frontostriatal circuitries, which are affected in people with PD in relation to the stage of the disease (Bodden et al., 2010). In particular, at early stages PD affects the head of the caudate nucleus, an area belonging to the Dorsolateral Frontostriatal circuitry (DLFS) and involved in cognitive ToM tasks. With the progression of the disease, the depletion of dopamine also affects the Orbital Frontostriatal circuitry (OFS), with the involvement of the affective sub-components of ToM.

Considering that the ToM profile of individuals with PD is relatively characterized as compared to that of MCI, in the current study we sought to compare ToM abilities in these two populations. It was reasoned that a comparison between two non-demented populations, i.e. MCI and early PD, could be helpful in characterizing the different profile of ToM functioning in relation to different neuropathological processes, also in the early stage when social cognitive impairment might be subtle and hardly to detect (Moreau et al., 2015). Deficits in cognitive and/or affective subcomponents of ToM might be a core feature of the early stages of such two neurological disorders, with a significant impact on daily living of patients, especially on their quality of life and social interactions (Henry et al., 2016; Yu & Wu, 2013).

To the best of our knowledge, no study so far has explored affective Vs. cognitive ToM functioning among patients with MCI using the Yoni task, and no studies have directly compared these two dimensions of ToM functioning in MCI and PD, two neurodegenerative conditions without severe cognitive impairment and dementia in the early stage. To this end, we investigated both cognitive and affective dimensions of mentalizing ability by using for the first time the computerized Italian version of the Yoni task (Shamay-Tsoory & Aharon-Peretz, 2007), together with a ToM battery that includes both cognitive and affective paper-pencil tasks commonly used in the research with adults and elderly individuals (Castelli et al., 2010). We hypothesized that people with MCI and PD would exhibit different, specific patterns of ToM impairment according to the different pathological process involved in these two neurodegenerative diseases.

Methods/Design

Participants and clinical assessment

A total of 48 participants were consecutively recruited from the Don Carlo Gnocchi Foundation, IRCCS S. Maria Nascente in Milan (Italy). Participants included 16 outpatients diagnosed with amnestic Mild Cognitive Impairment [aMCI group: mean (SD) age: 75.88 (3.65) years; range 67-80 years; male:female ratio 8:8; mean (SD) education: 11.81 (2.40) years], 14 outpatients with Parkinson's disease [PD group: mean (SD) age: 68.21 (7.96) years; range 52-78 years; male:female ratio 13:1; mean (SD) education: 14.21 (3.44) years] and 18 healthy controls [HC group: mean (SD) age: 74.06 (3.39) years; range 69-80 years; male:female ratio 8:10; mean (SD) education: 12.00 (3.24) years]. Table 1 shows the demographic and clinical characteristics of the samples in more detail.

The inclusion criteria for people with aMCI were the following: 1) diagnosis of mild AD or MCI due to AD, according to the recommendations of the National Institute on Aging (Albert et al., 2011; McKhann et al., 2011;) and the DSM 5 diagnostic criteria (American Psychiatric Association - APA 2013); 2) normal global cognitive function, as determined by both the CDR scale (Morris, 1993; CDR with at least a 0.5 in the memory domain) and the Mini Mental State Examination score (MMSE score ≥ 24; Folstein, Robins, & Helzer, 1983), corrected for gender, age and years of education according to Italian normative data (Measso et al., 1993); 3) memory complaint, confirmed by an informant; 4) abnormal memory function, documented by an extensive neuropsychological examination ; 5) no impairment in functional activities of daily living as determined by a clinical interview with the patient and the informant; 6) absence of cerebral vascular disease, as evidenced by Magnetic Resonance Imaging, or psychiatric illnesses, with particular attention to excluding participants with a history of depression (Hamilton Depression Rating Scale score ≤ 12; Hamilton, 1960); 7) age over 65 years; and 8) school attendance ≥3 years.

The inclusion criteria for the PD group were: 1) diagnosis of probable PD, according to Gelb's clinical diagnostic criteria (Gelb, Oliver, & Gilman, 1999); 2) Mini Mental State Examination score within the normal range (MMSE cut-off score 23.80; Folstein, Folstein, & McHugh, 1975) corrected for gender, age and years of education according to Italian normative data (Measso et al., 1993); 3) scores on Hoehn & Yahr (H&Y; Hoehn & Yahr, 1967) less than 2.5; 4) absence of psychiatric and other neurologic illnesses, in particular, visual hallucinations, severe depression or autonomic failure; and 5) antiparkinsonian treatment at a stable dosage during the three months prior to study entry.

The group of healthy controls (HC) consisted of age-matched volunteers with MMSE scores greater than or equal to 26 (Folstein, Folstein, & McHugh, 1975) who attended the Don Carlo Gnocchi Foundation. They were screened according to their clinical history in order to exclude major systemic, psychiatric or neurological illnesses.

Exclusion criteria for all participants were: 1) the presence of visual or auditory deficits; 2) a positive history of psychiatric disorders or behavioral problems; 3) the presence of other neurological conditions, cardiovascular diseases or cerebrovascular diseases; 4) a MMSE (Mini Mental State Examination, Folstein, Folstein, & McHugh, 1975) score ≤23.80, in order to exclude participants with dementia.

The study conformed to the ethical principles of the Helsinki Declaration (1975, revised in 2008), with approval from the local ethics committee (Don Carlo Gnocchi Foundation, Milan). Informed written consent was obtained from all participants before the study began.

Neuropsychological and Theory of Mind assessment

Participants underwent a conventional neuropsychological assessment and a traditional paper-pencil ToM evaluation. In addition, a computerized task (the Yoni task) was used to assess affective and cognitive dimensions of ToM.

Neuropsychological assessment

During the neuropsychological examination, we administered the Montreal Cognitive Assessment test (MoCA; Santangelo et al., 2015) as a measure of global cognitive level. According to the theoretical model proposed by Santangelo and colleagues (2015), the total raw score of the MoCA test was divided into 12 subtasks exploring the following cognitive domains: Memory (score range 0-5), Visuo-Spatial Abilities (score range 0-4), Executive Functions (score range 0-4), Attention (score range 0-6), Language (score range 0-6) and Temporal/Spatial Orientation (score range 0-6). The total score of the MoCA test was also considered (score range 0-30). Adjusted and equivalent scores for the total MoCA score and for each cognitive domain subscores were provided (except for the Memory domain) according to the normative data in the Italian population sample (Santangelo et al., 2015).

Paper-pencil ToM tasks

ToM reasoning was assessed with a conventional paper-pencil battery specifically designed for research on adults and older individuals (Baglio et al., 2012; Castelli et al., 2010, 2011). For a detailed description of the tasks, please refer to Castelli et al. (2010).

The battery included:

- The *Deceptive Box Task* (Perner, Leekam, & Wimmer, 1987), which assesses the first level of false belief understanding (first-order false belief task). A closed box of candies is shown to the participant, the content of which has been previously substituted with staples. The examiner asks the participant what the closed box contains; then, the box is opened, the real content is shown and the box is closed again. At the end, the participant is asked to predict what another person would say if shown that closed box (first-order false belief question), to justify this answer, and to say what he/she had thought before discovering the real content (first- order own false belief question). Two control questions are also provided. Each question is scored 1 if the answer is correct and 0 if the answer is wrong (range 0-5).

- The *Look-Prediction* and the *Say-Prediction* tasks (Astington, Pelletier, & Homer, 2002; Liverta Sempio et al., 2005; Sullivan, Zaitchik, & Tager-Flusberg, 1994), which assess the second level of false belief understanding (second-order false belief tasks). The participant has to predict where a character in the story thinks another character would look for a hidden object (look-prediction) or what a character thinks the other one would say about a hidden object (say-prediction). Both tasks require participants to answer a total of five questions: two control questions (one memory item and one reality item) and three mentalistic questions (a first-order false belief question, a second-order false belief question and justification of the second-order false belief question). Each question is scored 1 if the answer is correct and 0 if the answer is wrong (range 0-5).
- The *Reading the Mind in the Eyes test* (RME test, Baron-Cohen et al., 2001), which assesses affective ToM. The test consists of 36 pictures of the eye region taken from different human faces. Participants have to infer what the character is feeling and choose a word that describes the character's mental state from four mental states written under each picture. In addition, the Gender Test was used as a control condition in order to test basic visual face discrimination ability, such as gender attribution. Each item is scored 1 if the answer is correct and 0 if the answer is wrong (range 0-36);
- A selection of four stories from the *Strange Stories* task (Happè, 1994; Happè, Brownell, & Winner, 1999; Italian translation by Mazzola and Camaioni, 2002) to assess a more advanced level of ToM reasoning about the social world and a selection of four physical stories used as a control condition. Each question received a score of 0 for wrong answers, 1 for partially correct/incomplete answers and 2 for correct answers (range 0-2 for each question). The global scores of the four "ToM stories" and of the four physical stories ranged from 0 to 8.

Yoni task

Cognitive and affective ToM abilities were assessed with the Italian translation of the *Yoni task* (Shamay-Tsoory & Aharon-Peretz, 2007). The task consists of 98 trials, each showing a face named “Yoni” (“Gianni” in the Italian version of the task) and four colored pictures surrounding the face, one in each corner of the screen, and referring to various semantic categories (for example, fruit, animals, chairs, means of transport) or faces. The participant is required to choose the correct image to which Yoni is referring based on a sentence that appears on the top of the screen and on some available cues, such as Yoni’s eye gaze or facial expression or the eye gaze/facial expression of faces around him. Participants were instructed to choose the answer they thought to be correct by pointing to it with the computer mouse as fast as they could. Only one of the four alternatives is correct. The items differ in the complexity of the meta-representation they require, i.e., first- or second-order levels, and in the assessment of affective ToM (*Yoni likes*…), cognitive ToM (*Yoni is thinking* of…) or a physical (control) condition (*Yoni is close to*…). First-order cognitive and affective ToM items require participants to infer Yoni's mental state. In particular, in the cognitive condition both Yoni’s facial expression and the sentence at the top of the screen are emotionally neutral (for example, “*Yoni is thinking of...*”), while in the affective condition, all cues provide relevant affective (both positive and negative) information (for instance, “*Yoni loves…”/”Yoni doesn’t love...*”). In the second-order items, participants must understand the interaction between Yoni’s mental state and each of the four images around him (in the second-order items, the four stimuli always consist of faces). For example, the sentence “*Yoni is thinking of the chair that….wants*” requires a second-order cognitive inference, while the sentence “*Yoni loves the animal that…loves*” requires a second-order affective inference. The items in the physical condition only require participants to think about the physical attributes of the character. These items were added in order to ensure that participants understood the instruction and were not responding automatically only to the eye gaze. Following Shamay-Tsoory & Aharon-Peretz (2007), the performance was rated for accuracy. Each item was scored 1 if the answer was correct and 0 if the answer was wrong. Thus, the total score on the Yoni task (Yoni TOT) ranged from 0 to 98. For each participant, the scores gained from each sub-category were summed in order to obtain four sub-totals: the total of first-order cognitive items (COG1, range 0-12), the total of second-order cognitive items (COG2, range 0-24), the total of first-order affective items (AFF1, range 0-12) and the total of second-order affective items (AFF2, range 0-36). No participants were excluded from the study because of an accuracy rate lower than 50% on the physical condition.

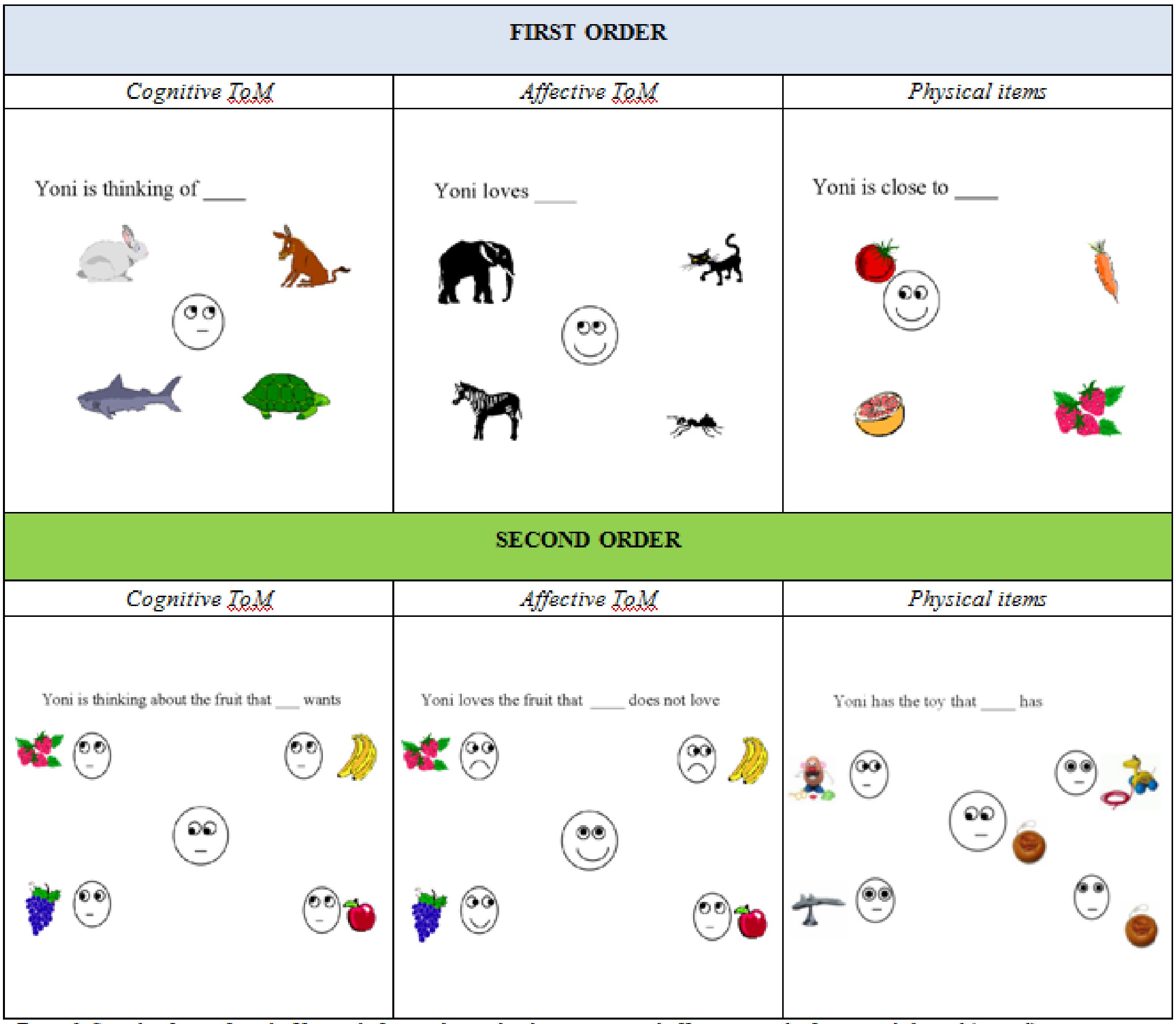

Figure 1: Sample of items from the Yoni task: first- and second-order, cognitive and affective mental inference and physical (control) items.

Statistical analysis

All statistical analyses were conducted using the IBM SPSS Statistics software, version 22. A *p*-value < 0.05 was considered statistically significant. Group comparisons of demographic variables of the three groups were computed using analyses of variance (ANOVA). Bonferroni *Post-hoc* tests were also computed to compare each diagnostic group with the HC group. Consequently, the Kruskal-Wallis H. test and the *Post-hoc* analyses corrected for multiple comparisons were used to: 1) compare scores obtained from the three groups both in the neuropsychological and in the ToM assessment (Tables 2-4); 2) compare the Reaction Times (RTs) within each group in the Yoni task according to the type of judgment (cognitive Vs. affective) and to the level of ToM reasoning (first- and second-order).

Results

Participants and clinical assessment

Table 1 shows the demographic data of the three samples. According to the specific clinical and epidemiological features of the diagnostic groups, age differed significantly between the MCI group and the PD group. In particular, the MCI group was older than the PD group (p=.001) and the PD group was younger than the HC group (p<.05). Instead, the three groups were comparable for the level of education, as we found no significant differences in the level of education among the groups (p=.069).

The PD group scored between stages 1 and 2.5 on the Hoehn and Yahr (H&Y) scale (1967), indicating that participants were at a mild stage of the disease. None reported any cognitive problems or any evidence of deficits in their daily living activities. None of the patients reported changes in medication during the period of at least three months before enrollment and none was taking any additional psychotropic drug. Patient mean (SD) on the Unified Parkinson's Disease

Rating Scale (UPDRS) evaluated immediately before the study began was 20.14 (15.17), and scores ranged from 4 to 44.

Table 1: Demographic and clinical characteristic of the sample.

* Significant differences between the MCI group and the PD group and between the PD group and the HC group.
[#] Significant differences between the MCI group and the PD group and between the MCI group and the HC group

Neuropsychological assessment

		aMCI (n=18)	*PD (n=14)*	*HC (n=18)*	Pvalue[a] (ALL)
Age *(years)*	*Mean(SD)*	75.88 (3.65)	68.21 (7.96)	74.06 (3.39)	0.001*
Education *(years)*	*Mean(SD)*	11.81 (2.40)	14.21 (3.44)	12.00 (3.24)	0.069
Gender *(M:F)*		8:8	13:1	8:10	-
MMSE	*Mean(SD)*	28.21 (1.56)	29.50 (0.10)	29.35 (1.20)	0.014[#]
H&Y	*Median(range)*	-	1.00 (1.00,2.50)	-	-
UPDRS	*Mean(SD)*	-	20.14 (15.17)	-	-

All patients scored within the normal range on the total score of the MoCA test according to the equivalent scores (Santangelo et al., 2014) (Table 2). However, a significant difference emerged between groups on the global cognitive level assessed with the MoCA test (X^2=14.32, p=.001). In particular, the MCI group scored lower compared to the HC group (p=.001), while no significant differences emerged between the PD group and the HC group and between the MCI group and the PD group (Table 2)

As regards the single cognitive domain subscores, significant differences emerged among groups in the Executive Functions subscore (X^2= 7.59; p<.05), in the Memory subscore (X^2= 6.15; p p<.05) and in the Language subscore (X^2=8.05, p<.05). Post hoc tests revealed that the PD group obtained significantly lower performances in the Executive Functions subscore compared to the HC group (*p*=0.04), and that the MCI group scored lower compared to the HC group both in the Memory subscore (*p*=0.041) and in the Language subscore (*p*=0.02).

	aMCI (n=18)	*PD (n=14)*	*HC (n=18)*	**Pvalue[a]** (ALL)	**Pvalue[b]** (MCIvsHC)	**Pvalue[c]** (PDvsHC)	**Pvalue[d]** (MCIvsPD)
Neuropsychological tests							
MoCa total score	23.91 (22.60,25.22)	25.29 (23.84,26.30)	27.08 (25.02,29.14)	.001	.001	.112	.397
Domain subscores							
Memory	0.00 (0.00,3.00)	2.50 (1.00,4.00)	3.00 (2.00,4.00)	.046	.041	1.00	.461
Visuo-spatial abilities	3.56 (3.01,4.00)	3.65 (2.62,3.90)	3.96 (3.64,4.00)	.051	-	-	-
Executive functions	3.15 (2.77,3.84)	3.09 (2.79,3.74)	3.82 (3.35,4.00)	.019	.082	.031	1.00
Attention	5.89 (5.27,6.00)	5.89 (5.46,5.89)	5.98 (5.89,6.00)	.184	-	-	-
Language	4.91 (3.88,5.74)	5.39 (5.09,5.79)	5.88 (5.29,5.93)	.019	.019	.195	1.00
Visual-spatial Orientation	6.00 (6.00,6.00)	6.00 (5.98,6.00)	6.00 (6.00,6.00)	.509	-	-	-

Table 2: Neuropsychological tests. Group characteristics and non-parametric comparisons. Scores were reported as median and interquartile range. Scores are adjusted for age and educational level.

Pvalue[a] test for overall comparison (MCI vs HC vs PD) ; Pvalue[b] test for MCI vs HC; Pvalue[c] test for PD vs HC; Pvalue[d] test for MCI vs PD. Group comparisons were computed with the Kruskal-Wallis H. test; pairwise comparisons were computed with Bonferroni *post hoc* test.

Paper-pencil ToM tasks

All participants exhibited good performance on the control tasks, i.e., the gender test and the physical stories. Two participants of the PD group who scored 0 on both the control questions of the Look-Prediction and on both the control questions of the Say-Prediction tasks were excluded from the analysis of those tests.

Our results show no significant differences among groups in the Deceptive Box task, in the Look-Prediction task and in the Say-Prediction task (Table 3). Notably, we found significant between-group differences in the most advanced ToM tasks, i.e. in the RME test (X2=11.71, p<.005) and in the Strange Stories task (X2=6.87, p<.05). In particular, pairwise comparisons revealed that the MCI group had lower performance than the HC group both on the RME test (p<.005) and on the Strange Stories task (p<.05), while no significant differences emerged between the two clinical groups (MCI and PD) and between the PD group and the HC group (Table 3).

	aMCI (n=18)	***PD (n=14)***	***HC (n=18)***	**Pvalue[a]** (ALL)	**Pvalue[b]** (MCIvsHC)	**Pvalue[c]** (PDvsHC)	**Pvalue[d]** (MCIvsPD)
Paper-pencil ToM tasks							
Deceptive Box task	5.00 (5.00,5.00)	5.00 (5.00,5.00)	5.00 (5.00,5.00)	1.00	-	-	-
Look-Prediction task	3.00 (3.00,3.00)	3.00 (2.50,3.00)	3.00 (3.00,3.00)	.118	-	-	-
Say-Prediction task	2.00 (1.00-3.00)	1.00 (1.00,2.50)	3.00 (1.00,3.00)	.070	-	-	-
RME test	19.50 (16.25,21.00)	21.00 (18.00,25.25)	26.00 (21.25,27.25)	.003	.002	.136	.660
Strange Stories task	5.00 (4.25,5.75)	7.00 (4.50,7.00)	7.00 (5.00,8.00)	.032	.028	1.00	.351

Table 3: Paper-pencil ToM tests. Group characteristics and non-parametric comparisons. Scores were reported as median and interquartile range. Scores are adjusted for age and educational level.

Pvalue[a] test for overall comparison (MCI vs HC vs PD) ; Pvalue[b] test for MCI vs HC; Pvalue[c] test for PD vs HC; Pvalue[d] test for MCI vs PD. Group comparisons were computed with the Kruskal-Wallis H. test; pairwise comparisons were computed with Bonferroni *post hoc* test.

Yoni task

Accuracy

No differences emerged between groups for the control items (physical condition) of the Yoni task (Table 4). However, a significant between-group difference emerged on the total score of the Yoni task (TOT/98, X^2=8.95, p<.05). In particular, the MCI group scored lower compared to the HC group (*p*<.05), while no differences emerged between the PD group and the HC group and between the two clinical groups.

While no between-group differences emerged on the first-order affective items (AFF1), we found significant between-group differences on the second-order affective items (AFF2, X^2=6.46, p<.05). In particular, the MCI group scored lower compared to the HC group (p<.05), while no significant differences emerged between the two clinical groups and between the PD group and the HC group.

As for the first-order cognitive items (COG1), we found a significant difference across groups (X^2=12.50, p<.005). In particular, the MCI group exhibited significantly lower performance compared to both the HC group (p<.005) and the PD group (p<.05), while no differences emerged between the PD group and the HC group. The results obtained for second-order cognitive items (COG2) are similar to those for second-order affective items reported above. Significant differences emerged between the groups (X^2=7.26, p<.05), with the MCI group scoring lower than the HC group (p<.05), while no significant differences emerged between the two clinical groups and between the PD group and the HC group.

3.4.2 Reaction Times (RTs)

Our results showed no significant differences in the RTs across groups, both in the affective/cognitive first-order items (AFF1, *p*=.39; COG1, *p*=.11), and in the affective/cognitive second-order items (AFF2, *p*=.14; COG2, *p*=.30) of the Yoni task.

	aMCI (n=18)	PD (n=14)	HC (n=18)	Pvalue[a] (ALL)	Pvalue[b] (MCIvsHC)	Pvalue[c] (PDvsHC)	Pvalue[d] (MCIvsPD)
Yoni task							
AFF1	12.00 (11.00,12.00)	12.00 (11.00,12.00)	12.00 (11.00,12.00)	.559	-	-	-
AFF2	24.50 (19.25,30.00)	28.00 (24.75,32,25)	30.00 (27.50,32.25)	.040	.037	1.00	.298
COG1	11.00 (9.50,12.00)	12.00 (11.75,12.00)	12.00 (12.00,12.00)	.002	.002	1.00	.027
COG2	16.50 (13.00,17.75)	20.50 (16.75,22.25)	21.00 (14.00,23.00)	.026	.041	1.00	.091
Total Score	76.00 (67.00, 84.75)	83.50 (80.75,90.50)	88.50 (79.75,92.00)	.011	.016	1.00	.059

Table 4: Yoni task. Group characteristics and non-parametric comparisons. Scores were reported as median and interquartile range. Scores are adjusted for age and educational level.

Pvalue[a] test for overall comparison (MCI vs HC vs PD) ; Pvalue[b] test for MCI vs HC; Pvalue[c] test for PD vs HC; Pvalue[d] test for MCI vs PD. Group comparisons were computed with the Kruskal-Wallis H. test; pairwise comparisons were computed with Bonferroni *post hoc* test.

Discussion

The aim of the present study was to characterize ToM functioning among two non-demented neurodegenerative diseases characterized by different neuropathological processes at early stages: the MCI group, predominantly typified by cognitive symptoms, and the PD group, primarily characterized by motor symptoms. Both clinical conditions were also compared to a group of healthy control participants (the HC group). We administered the Yoni task to evaluate both cognitive and affective, first- and second-order dimensions of ToM, in conjunction with a paper-pencil ToM battery commonly used to evaluate ToM in the life-span.

Our results showed that, on the paper-pencil ToM tests, all groups scored above the cut-off. More specifically, the performances on the Deceptive Box Task (first-order false belief task), the Look-Prediction task and the Say-Prediction task (both first- and second-order false belief tasks) were similar for all three groups, while some differences emerged in the more advanced ToM tasks. The MCI group scored lower compared to the HC group on the RME test and on the Strange Stories task. These tasks imply higher cognitive load to be performed, especially high verbal and memory load, which may be impaired in people with MCI. These results add further evidence to the state-of-the-art literature about ToM functioning in people with MCI, which is still quite controversial. In fact, our results on the RME test are in line with Poletti and Bonuccelli (2013), who reported low performance among people with MCI in inferring affective mental states as assessed with the RME test. Yet, these results are not in line with previous results obtained by Baglio et al. (2012), who found no impairments on an RME test administered in a reduced version for a fMRI paradigm. With respect to the Strange Stories task, our results are not in line with the previous results of Baglio et al. (2012) who found no impairment in aMCI in this task that examines the social implications of ToM reasoning. Probably, this puzzling picture can be explained referring to two elements. The first concerns the intrinsic variability of the clinical samples due to the presence of different diagnostic criteria, which are all scientifically grounded but not univocal. The second element refers to the high variability of the ToM tasks used in each study. In fact, various types of tasks are used to measure the same construct (for example, false belief reasoning), and the same task can be adapted according to the research paradigm (for example, paper-pencil vs. functional magnetic resonance imaging paradigm). The still controversial picture about ToM functioning among MCI populations also emerges from two recent studies with different ToM tasks. Moreau et al. (2015) found ToM impairments in the very early stages of MCI, even in real social interaction evaluated through video clips and on the Referential Communication task (Champagne-Lavau et al., 2009). On the other hand, Dodich et al. (2016) found that the MCI group had no impairments in ToM competence as evaluated by the Story-Empathy task, a non-verbal task measuring the ability to infer the intentions and emotions of others (Dodich et al., 2016).

In contrast with the conflicting results of ToM abilities in MCI the pattern of ToM abilities in PD is relatively established. Therefore, comparing MCI with PD group both on classical paper-pencil ToM tasks and on the Yoni task may help to clarify the pattern of ToM impairment among people with MCI. In line with previous studies (see Poletti et al., 2012 for a review), we show here that the PD group exhibits impairment on the more advanced ToM tasks (the RME test and the Strange Stories task), scoring between healthy elderly people and people with MCI. In fact, no differences emerged on either task between the MCI and the PD groups and between the PD group and the HC group. Thus, it also seems that people with PD show initial decay on advanced ToM tasks that evaluate the emotional components of ToM compared to the HC group, although the difference is not significant.

A better understanding of ToM functioning in MCI and PD is offered by the results of the Yoni task, which allows us to analyze both the complexity of ToM reasoning (first-and second-order) and the cognitive vs. affective dimensions of this construct. First, our results showed that people with MCI scored lower on the global score of the Yoni task compared to the HC group. In order to better assess where the MCI group fails, we considered the different components of the Yoni task. We found no significant difference among groups on the first-order affective items (AFF1), indicating that all patients were not impaired in this basic condition. This result can be explained in relation to the brain areas affected in both neurodegenerative diseases, and according to the stages of the diseases. In fact, both MCI and PD were at the early stage of the disease, therefore we can assume that the pre-frontal regions have not yet been affected by the disease, thus leaving the affective condition substantially preserved.

On the contrary, in the first-order cognitive condition (COG1), the MCI group exhibited the worst performance compared to the HC and the PD groups, while no significant difference emerged between the HC and PD groups. This result is quite interesting, given that people with MCI showed no impairment in the classical paper-pencil first-order false belief tasks. So, it seems that the Yoni task is able to detect early ToM impairment at the first-order levels of cognitive ToM reasoning, whereas classical paper-pencil false belief tasks are not able to detect such impairments. Moreover, the performance in the Yoni task indicated a decrease in the first-order cognitive scores only in the MCI sample, which is characterized predominantly by cognitive symptoms. On the second-order cognitive and affective items (COG2 and AFF2) we found a pattern of results similar to those on the Eyes Test and the Strange Stories test, with a decrease in ToM functioning observed among people with MCI and an initial decay in PD patients. These results seem particularly interesting because they offer the possibility to define the pattern of ToM impairment in the MCI group and the PD group at different levels. In fact, the MCI group showed the worst performance on the first-order cognitive items compared to both the HC and the PD groups, and a lower performance on the second-order cognitive and affective items compared to the HC group only. Thus, the Yoni task highlighted the decay of both the basic level of cognitive ToM reasoning and of the more complex ToM inferences (both cognitive and affective second-order levels of reasoning) among MCI patients, while the first level of affective ToM seems to be preserved. The Yoni task also appears to enable detecting an initial decay of advanced ToM performance in the PD group. So far, only Bodden et al. (2010) have investigated affective and cognitive dimensions of ToM in PD using the Yoni task. They showed that PD patients exhibited low scores on both the affective and cognitive second-order ToM subscales, and that such impairment was not related to cognitive deficits. In the present study, the performance of the PD group on the Yoni task was not significantly different from that of the HC group. The performance of the PD group also did not differ significantly from that of the MCI group, indicating that the PD patients were showing reduced performance in this task, scoring between people with MCI and healthy control participants. The absence of significant differences between the PD group and the HC group could be explained by different clinical and epidemiological features of the two samples. Our PD sample was at a mild stage of the disease, scoring between stages 1 and 2.5 on the Hoehn and Yahr (H&Y) scale (Hoehn & Yahr, 1967), while the PD sample in Bodden's study was at a mild to moderate stage of the disease, with an

H&Y median of 2.5, ranging from 1 to 3. However, it is important to point out that the level of accuracy on both the affective and cognitive items of the Yoni task in our study and in the research of Bodden et al. (2010) was well above the cut-off, so the performance of both the PD groups on the Yoni task was substantially preserved.

The selective impairment of the cognitive dimension on one side and of the second-order level of ToM reasoning on the other side could be interpreted in the light of cognitive demand involved in those tasks. In fact, even though the strong debate in the literature regarding the relationship between ToM and executive functioning still has some discrepancies, it seems that the typical decline in ToM due to aging could be mediated by alterations in executive functions (Kemp et al., 2012). This point may be more relevant in neurodegenerative pathologies, where the progression of the disease mainly affects the brain structures involved in high cognitive functions. In the present study, the pattern of ToM decay in MCI and the initial ToM impairment in PD could be partially interpreted in the light of the neuropsychological profile of each clinical group. Our neuropsychological assessment provides a picture of cognitive functioning which is congruent with the specific phenotypes of the two groups at the early stages of the disease. In fact, although all participants were above the cut-off on the global cognitive task, we found significant differences between groups both in the total score of the MoCA test and in the specific cognitive domains. In particular, the significant decrease of ToM performance observed in people with MCI could be interpreted in the light of an initial decline in the global cognitive level, in particular in the memory function and language skills compared to healthy controls. Furthermore, the PD group showed worse performance only in the "Executive Functions" subscore of the MoCA test compared to the healthy controls and this might explain the selective, early decrease in the performance of the more advanced ToM tasks, in which the executive functioning might play a major role.

Conclusion

Deficits in social cognition represent a core feature of many neurodegenerative disorders and may have a significant impact on mental health and wellbeing (Henry et al., 2016). For this reason, its assessment in the clinical setting has gradually gained importance in addition to the classical neuropsychological assessment. In fact, an assessment of ToM for Major Cognitive Disorders was introduced in the DSM-V (2013), and Adenzato & Poletti (2013) have warmly suggested that mentalizing tasks should be introduced into standard neuropsychological assessments.

At the same time, it is important to notice the great variety of ToM tasks that are usually employed to test ToM in neurodegenerative pathologies, thus leading to contradictory findings. The present study has offered preliminary evidence of the capacity of the Yoni task to detect different patterns of ToM deficits among people with MCI and to highlight an initial decay in ToM functioning among people with PD. The advantage of the Yoni task is that it provides an opportunity to highlight different levels of ToM deterioration at an earlier stage, i.e., in the absence of dementia, across different neurodegenerative pathologies.

Limitations of the study

The present study represents a preliminary investigation of affective and cognitive ToM in pre-demented populations with the Yoni task. The significant age differences between the MCI group and the PD group may constitute a possible limitations of this study. This difference may have influenced the comparison between the two clinical groups, especially on the ToM tasks where adjusted scores according to normative data are not provided. However, such differences could be explained in light of the different clinical features of these two neurodegenerative pathologies in their early stages, and particularly the mean age of onset. In fact, both clinical conditions are age-related, but the mean age of onset varies significantly: the mean age of onset for PD is estimated to be in the early-to-mid 60s (Inzelberg, Schechtman, & Paleacu, 2002), while MCI appears to become more prevalent in individuals aged 70 years and older (Petersen et al., 2009). Future studies should expand the sample size in order to further strengthen this pattern of results and to provide a more robust knowledge of ToM changes in age-related neurodegenerative pathologies, which in turn could pave the way for devising possible interventions to enhance ToM functioning across the life-span.

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Chapter 5

General Discussion

The clinical assessment of Theory of Mind:

future opportunities in social cognitive research

Each of the three Chapter developed in this thesis highlighted that social cognitive functioning, and in particular, ToM reasoning could be significantly affected by the neuropathological process of different neurodegenerative diseases, also in their early stage.

The aim of the present work was to explore ToM performance in pathological aging from different perspectives, in the light of the more recent literature on this topic (Cotter et al., 2017; Henry et al., 2016): 1) ToM performance as a potential marker for the disease progression (Chapter 2 and 3); ToM performance as a possible outcome measure of multidimensional interventions (Chapter 3); ToM tasks as an assessment tools able to discriminate between successful and unsuccessful aging (Chapter 3) and between different neurodegenerative pathologies (Chapter 4).

Theory of Mind as a marker for the disease progression

The most recent literature data show that social cognitive assessment offers the potential to examine the disease progression. There is evidence that social cognitive impairment characterizes the early stage of many clinical conditions, including the early stage of dementia (Bora et al., 2017), and that ToM deficits get worse with the progression of the disease (Bora et al., 2015, 2016). Such impairment affects the ability to form and maintain social relationships, leading to poor social and occupational functioning and reduced quality of life. For this reason, ToM performance could be considered a critical, longitudinal predictor of clinical and functional outcome in people with neurodegenerative conditions. However, to the best of my knowledge, no studies investigated the evolution of ToM competences across time so far. Chapter 2 and 3 of the present thesis aimed to fall this gap assessing the evolution of ToM competences over time in people with aMCI.

In Chapter 2 we conducted a pilot study aimed to explore the possible connections between the performance on cognitive and affective ToM and the cognitive functioning of people with aMCI in a longitudinal perspective. Our preliminary results showed that aMCI subjects were substantially preserved on both their cognitive and ToM profile at the follow-up if compared to the baseline. However, despite this general preserved cognitive and social functioning, we observed a decreased (although not significant) second order cognitive ToM performance from the baseline to the follow-up, while no differences emerged in the first order cognitive ToM. On the other hand, an opposite statistical trend emerged regarding the affective ToM, which tends to improve over time.

This result could be considered in the light of the still open debate concerning the relationship between ToM and cognitive functions (Aboulafia-Brakha et al., 2011). In fact, it seems that a high neuropsychological performance supports the cognitive ToM reasoning but not the affective components of ToM evaluated with the RME test. The differential pattern of evolution in cognitive and affective ToM emerges prominently also in Chapter 3. The principal aim of this study was to investigate, in a longitudinal perspective, potential changes of ToM abilities in aMCI sample involved in a Multi-Stimulation Treatment at Home (MST@H) program aimed to reinforce motor, cognitive and social skills (Baglio et al., 2014). The results obtained from the longitudinal monitoring of the aMCI group could help us clarify the relationship between cognitive functioning and ToM performance emerged in Chapter 2. In fact, in the present study, we found that the cognitive ToM changes were related to the cognitive modifications induced by treatment in aMCI subjects. In particular, we observed that the multidimensional intervention had a statistically significant impact on some cognitive abilities (memory and executive functions), and on the cognitive component of ToM, since we observed a significant improvement of the Strange Stories task 12 months apart (T2). This result is foreseeable, given that the Strange Stories task is presumed to assess more cognitive ToM aspects and we observed an improvement in the global cognitive level of the MCI subjects at the T2 follow up.

On the contrary, the ability to infer affective mental states from the eye gaze remains stable over time, and within the normal range, as also demonstrated by previous research (Phillips et al., 2002; Castelli et al., 2010, Cabinio et al., 2015). This is probably due to the minimal involvement of the general cognitive abilities, and in particular of the executive functioning in the RME test (Sandoz et al., 2014). However, it has been demonstrated that the RME performance is at least partially influenced by language skills, probably as a consequence of the verbal components of the task (Peterson and Miller, 2012). In Chapter 3, the language skills remain unchanged over time, perhaps contributing to maintain high level of RME performance at the T2 follow-up. This assumption is supported by or previous work investigating the RME performance in relation to the structural connectivity changes in healthy aging (Cabinio et al., 2015), which demonstrated that the volume reduction in the premotor cortex, the inferior frontal gyrus, the insula and the superior temporal gyrus, may result in difficulties to infer other's mental states through the eye gaze. However, the recruitment of additional neural circuits, such as bilateral language areas, might help to preserve the RME performance in elderly subjects (Cabinio et al., 2015; Castelli et al., 2010). Thus, although questioned[3], the RME test could be considered a useful measure for the longitudinal assessment of the affective dimension of ToM, being partially independent of the progressive cognitive worsening that is often observed in this clinical condition.

In conclusion, the longitudinal studies presented in this thesis (Chapter 2 and 3) suggested that both cognitive and affective dimensions of ToM represent potential longitudinal predictors of the disease progression, also in relation to intervention strategies aimed to counteract the conversion into blown dementia. A possible limitation of these studies was the relatively small number of aMCI subjects included in the analyses and the absence of a group of healthy controls in the first study. Additional research is needed to confirm these findings; however, both studies can be considered as the first step in the evaluation of ToM changes in the longitudinal perspective in aMCI samples.

ToM performance as outcome measure of multidimensional interventions

As highlighted in Chapter 2 and 3, ToM performance have the potential to serve as a marker of neural deterioration and disease progression in neurodegenerative conditions. However, Chapter 3 suggests that ToM could be a potential measure of efficacy of multidimensional interventions in rehabilitation contexts. In fact, as discussed above, in this study the multidimensional intervention (the MST@H program) had a statistically significant impact on some cognitive abilities (memory and executive functions), with long-term effects on executive functions, since the observed improvement was preserved after 12 months.

Interestingly, our results demonstrated that the multidimensional intervention had a positive influence also on the cognitive component of ToM since we observed a significant improvement of the Strange Stories task 12 months apart. On the contrary, our correlation analysis showed a

[3] The RME test is one of most popular test of affective ToM in adults. However, it is also one of the most contested task. In particular, it has been hypostasized that the RME test indexes emotion recognition rather than ToM ability (Oakley et al., 2016).

significant, inverse relationship between the Strange Stories task and the RME test. Specifically, the analyses revealed that individuals who got worse on the MoCA test (the MoCA – subjects) were the same one who showed increased RME scores, while people who have improved on their global cognitive level (the MoCA + subjects) showed different patterns of RME performance (both better and worse scores). Therefore, in this study, people whose cognitive functions did not benefit from the multidimensional intervention showed improved social competences, especially with regard to affective component of ToM. In this case, affective ToM seems to constitute a strong residual ability that compensates for cognitive decline. To further support the role of affective ToM as a compensatory pathway to counteract the conversion into dementia, we considered the behavior of the only subject who didn't respond to treatment and converted into AD. In this case, also the affective ToM decrease, together with the global cognitive *status* and the performance in the Strange Stories task. Future studies may investigate if the impairment of affective ToM could represent a marker of AD conversion also in relation to the cognitive reserve, which represents an important protective factor against the conversion in frank dementia (Stern, 2002, 2009).

In conclusion, these results highlight that, even if some aMCI subjects do not benefit from a multidimensional intervention from the cognitive perspective, they still obtain an advantage in other "non-cognitive" domains, such as their social skills. A possible limitations of this study is the imbalance in the number of "cognitive responder" (MoCA+) subjects, and "cognitive non-reponder" (MoCA-) subjects to the multidimensional intervention may have affected the comparisons between these two sub-groups. Moreover, it would have been useful to include a greater number of both HC and aMCI individuals not subjected to training but followed longitudinally in order to verify the trend over time of cognitive and affective ToM independently of the multidimensional intervention in both successful and unsuccessful conditions.

Given that social cognitive dysfunctions represent the main target of various types of non-pharmacological therapies, affective and cognitive ToM tasks should be included as outcome measures of multi-component interventions for people with mild-to-moderate dementia, in addition to the conventional cognitive measures. According to recent evidence suggesting that socio-cognitive skills are sensitive to interventions specifically developed to promote ToM performance in healthy older adults (Cavallini et al., 2015; Lecce et al., 2015), future studies should investigate if interventions specifically designed to improve ToM abilities such as Training ToM (Cavallini et al., 2015; Lecce et al., 2015) can enhance social functioning and autonomy in activities of daily life also of aMCI individuals. Our study did not consider if the observed ToM changes in the aMCI group were associated with changes in quality of life measures or other psychological/behavioural scales.

Future studies, in addition to filling these gaps, should also investigate if changes in cognitive and/or affective dimensions of ToM in relation to a multidimensional intervention is associated with changes in the neural network involved in social cognitive processes.

ToM tasks as assessment tools in the clinical practice

There is emerging evidence (Cotter et al., 2017) that ToM performance may serve as a screening tool among individuals with neurodegenerative conditions, serving as a marker for the disease onset, as highlighted in Chapter 3, and allowing the differentiation between different clinical conditions, as pointed out in Chapter 4.

Chapter 3 suggested that ToM tasks can be considered useful screening tools able to distinguish between people in the early stages of (or at risk to develop) dementia from healthy individuals. Our results showed that the aMCI subjects performed significantly worse than healthy controls (HC) in both advanced ToM tasks, the cognitive one (the Strange Stories task), and the affective one (the RME test). On the other hand, the two groups were comparable in the first-order mentalizing task (the Deceptive Box task). These results are in line with previous studies which demonstrated that the age-related impairment starts from the more advanced ToM reasoning, as highlighted in older adults (Duval et al., 2011; Kemp et al., 2012) and people with MCI (Bora et al., 2017).

This assumption has been corroborated by evidence primarily based on tasks that assess the cognitive component of ToM, Coherently, in the present study, MCI subjects showed a lower performance in the Strange Stories task compared with HC. This could be interpreted in the light of cognitive load implicated in this kind of ToM measure, which can be considered as a complex, high-order cognitive task requiring relatively undamaged cognitive functions. On the other hand, limited data are available on affective ToM in people with aMCI, and in particular on the RME test. Our results showed reduced RME performance in individuals with MCI compared to healthy controls, in accordance with Poletti and Bonuccelli, which reported statistically significant lower performance in inferring the affective mental states with the RME test in 20 aMCI subjects compared with 20 healthy controls (Poletti & Bonuccelli, 2013). Also, Baglio and colleagues (2012) found lower performance in a fMRI-adapted version of the RME test in aMCI subjects compared to controls, although such difference was not significant (Baglio et al., 2012).

Chapter 4 investigated the potential clinical contribution of ToM tasks for distinguishing between different neurodegenerative pathologies. In particular, the aim was to characterize ToM functioning between two non-demented neurodegenerative conditions characterized by different neuropathological processes at an early stage: the MCI group, predominantly characterized by cognitive symptoms, and the PD group, characterized mainly by motor symptoms. Both clinical conditions were also compared to a group of healthy controls (HC). We administered the Yoni task to evaluate both cognitive and affective, first and second order dimensions of ToM, in association with a set of paper-pencil ToM tasks traditionally used to evaluate ToM in the life-span. Our results showed that significant differences emerged only in the more advanced ToM tasks. In fact, the MCI group scored lower compared to the HC group on both the RME test and on the Strange Stories task, and the PD group showed an initial decay in the same tasks, scoring between healthy elderly people and people with MCI. A better understanding of ToM functioning in MCI and PD is offered by the results of the Yoni task, which highlighted a decrease of both the basic level of cognitive ToM and of the more complex ToM inferences (cognitive and affective second-order levels of attribution) among MCI patients, while the first order affective ToM appear to be preserved. The Yoni task was also able to detect an initial difficulty in advanced ToM tasks in the PD group.

In conclusion, the present study represents a preliminary investigation of affective and cognitive ToM in pre-demented populations with the Yoni task. Taking together, these results demonstrated that the Yoni task may represent a sensitive tool for detecting different patterns of ToM impairment across different neurodegenerative pathologies at early stages. However, this study had some limitations. First of all, the significant age differences between the MCI group and the PD group, which may have influenced the comparison between the two clinical groups, especially on the ToM tasks where adjusted scores according to normative data are not provided. Moreover, future studies should expand the sample size to provide more robust data about ToM changes in age-related neurodegenerative pathologies.

Conclusions

Our results emphasize the importance of the clinical assessment of ToM deficits in MCI condition with different purposes: 1) both cognitive and affective ToM tasks can be useful screening tools able to distinguish between people in the early stages of dementia and people at high risk to develop dementia (such as aMCI subjects) from healthy individuals; 2) ToM deficits can be considered potential longitudinal predictors of the disease progression, also in relation to intervention strategies against the conversion to dementia; 3) ToM performance can constitute valuable outcome measures of multidimensional interventions, together with cognitive, behavioral and functional measures.

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Curriculum Vitae

Federica Rossetto was born on 28th March 1987 in Como (CO), Italy. In 2010 she obtained the Bachelor's Degree in Psychological Sciences and Techniques at Università Vita-Salute San Raffaele (Milan). The thesis title was: "*Neurobiological bases of maternal attachment behaviour*" (Prof. D. Perani). In 2012 she obtained the Master's degree in Clinical Psychology at Università Vita-Salute San Raffaele (Milan), with an experimental thesis titled: "*Attachment style and functional magnetic resonance: an experimental study*" (Prof. Lucio Sarno; Dott. Sofia Crespi). The experimental study was performed at the department of neuroradiology, Center of Excellence for Magnetic Resonance (C.E.R.M.A.C) of the *San Raffaele Hospital* of Milan (Prof. A. Falini). After the one year of professional internship and the qualification to the profession of psychologist, she begin her Ph.D in the Research Unit on Theory of Mind at Catholic University of the Sacred Heart of Milan (tutor Prof. Castelli Ilaria). The research project, co-funded by the Don Gnocchi Foundation in Milan (Magnetic Resonance Laboratory, headed by Dr. F. Baglio), focuses on the study of Theory of Mind (ToM) in a lifespan perspective, especially in healthy adults and elderly and in people with neurodegenerative diseases.Currently, she is working as a post-doc in the MRI Laboratory at the IRCCS, Don Carlo Gnocchi Foundation of Milan. Her research interest concern the study of cognitive and affective components of ToM, of its neurobiological (using Functional Magnetic Resonance Imaging) and neuropsychological correlates, both in healthy subjects (adults and elderly) and in subjects with neurodegenerative diseases (in particular Mild Cognitive Impairment, Alzheimer's Disease and Parkinson's Disease), also in a longitudinal perspective; the study of Social Decision-Making processes in adolescents and young adults, in relation to the development of ToM abilities; design and implementation of research projects aimed at the motor and cognitive rehabilitation of people with dementia through the use of integrated home-based devices built on innovative technologies, in order to promote psycho-physical well-being of patients and their caregivers and to improve the quality of life of people with dementia, in particular Mild Cognitive Impairment and Mild/Moderate Alzheimer's Disease; Serious-games and virtual reality use in subjects with cognitive decline, both in neuropsychological assessment and in rehabilitative interventions.

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