

DOI: 10.21767/2171-6625.1000129

Theory of Mind in Unsuccessful Neurocognitive Aging: Preliminary Evidence from an aMCI-Converter to AD and From an aMCI Reverter to Near-Normal Cognition

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Received: Jun 15, 2016; **Accepted:** Jul 20, 2016; **Published:** Jul 25, 2016

Citation: Castelli I, Baglio F, Savazzi F, et al. Theory of Mind in Unsuccessful Neurocognitive Aging: Preliminary Evidence from an aMCI-Converter to AD and From an aMCI Reverter to Near-Normal Cognition. *J Neurol Neurosci*. 2016, 7: S3.

Abstract

Background: Two case reports of patients with Mild Cognitive Impairment (MCI) are presented with the aim to study Theory of Mind (ToM) in the evolution from successful to unsuccessful neurocognitive aging.

Methods: A 75-year-old man, six years of education, who converted to Alzheimer's Disease (AD) (Case 1), and a 60-year-old woman, five years of education, who reverted to near-normal aging (Case 2), are studied at Time 1 and at Time 2 after five years under the ToM profile and the neuropsychological profile (MMSE, Corsi-Span, Digit span forward/backward, delayed recall of Rey's complex figure task, test of Prose Memory, Naming Task, Token Task, Phonemic and Semantic Fluencies, Coloured Progressive Matrices, Attentive Matrices). Their results are compared with demographically matched healthy controls, and with AD patients for the former case and with MCI patients for the latter case.

Findings: Case 1 showed the typical pattern of conversion from the MCI condition to the AD condition, with a decline in general cognitive functioning, in long-term memory, in language understanding and in frontal functions. Regarding ToM, a decline in the most complex levels of ToM competence (Strange Stories) was observed. Case 2 showed a pattern of reversion from the MCI condition to a near-normal aging condition, both under the NPS and the ToM functioning.

Conclusion: Results are discussed in light of the possible protective factors (including ToM) operating against the switching to unsuccessful neurocognitive aging.

Keywords: Theory of mind (ToM); Mild cognitive impairment (MCI); Alzheimer's disease (AD); Case reports

Introduction

Theory of Mind (ToM), the ability to understand one's own and others' mental states and to refer to them to interpret, understand and predict behavior [1], is a key component of social cognition and a lifelong endeavor. The investigation of ToM has engendered great interest in developmental and clinical psychology fields. Nowadays, the focus has shifted on the evolution of ToM in adulthood and old age [2,3], showing that with advancing aging, ToM undergoes changes that lead to a progressive decline of its behavioral functioning as measured by various types of tasks, including the classical false belief tasks [4,5], social tasks such as the Strange Stories [6-8] and the Faux-Pas test [9], and affective tasks such as the Reading the Mind in the Eyes Test [10-12]. Besides the behavioral level, the neural networks underpinning ToM face important transformations with increasing age as well. There is strong evidence of the existence of a distributed neural network underlying ToM, which includes the posterior end of the superior temporal sulcus (pSTS) and the adjacent temporoparietal junction (TPJ), the temporal pole (TP), the medial prefrontal cortex, and the adjacent paracingulate cortex the precuneus, and the medial portions of the prefrontal cortex (PFC) - for reviews, see [13,14]. A shifting in the activations of ToM neural circuit has been reported with aging, with old adults presenting a more bilateral activation of frontal areas and a higher involvement of the linguistic components of the mirror neuron system (i.e., Brodmann Area (BA) 44) than young adults [12].

Given that ToM ability declines with aging, the study of its changes is relevant in understanding the processes associated with successful versus unsuccessful neurocognitive aging. Recent investigations regarding ToM in age-related clinical conditions, namely dementia and other neurodegenerative pathologies, showed specific impairments of this competence in relation to the progressive involvement of cortical and subcortical brain structures [3,15-17]. In Alzheimer's disease (AD) the progressive loss of ToM competence appears to occur

in reverse with respect to its acquisition [18-21]: the more advanced levels of ToM are damaged first – namely complex social reasoning and second order false belief reasoning – whereas the social understanding milestones are still generally preserved – namely first order false belief reasoning and intention detection. More interestingly, a decline of ToM has been reported already in people with Mild Cognitive Impairment (MCI) [22,23], the preclinical stage in the transition from a healthy condition to early AD condition [24-26]. People with MCI present with impairments in different cognitive domains affected by AD (e.g. episodic and semantic memory, language, attention...), but a preserved functional competence. Prominent memory impairment typifies amnesic MCI (aMCI), the subtype of people with MCI most vulnerable to convert to AD. Indeed, in a recent study, lower performances in two second order false belief tasks were observed in people with aMCI compared to healthy controls at a behavioral level [22]. Instead, no significant differences in behavioral performances on the Reading the Mind in the Eyes Test was found in aMCI compared to controls, even though a minor activation of some components (posterior end of the superior temporal sulcus and temporal pole) of the ToM neural circuit were observed in aMCI patients. This result was explained in light of neural compensation mechanisms involving the mirror neuron system (precentralgyrus-BA6; Broca area-BA44) and the frontal areas (middle and medial frontal cortex and anterior cingulate cortex).

The fact that ToM is a key-component of social cognition and that it affects every day social interactions and communications is relevant for the quality of life and for the well-being of the elderly. The growing attention in our society to the needs and resources of the older population combined with the scientific knowledge of ToM decline in aging, highlights the importance of studying the features of this ability both in successful and unsuccessful neurocognitive aging. In fact, an assessment of Theory of Mind for Major Cognitive Disorders was introduced in the DSM-V [27], and some authors [15] have warmly suggested that mentalizing tasks should be introduced into standard neuropsychological (NPS) assessments.

Notwithstanding such points, there is still a paucity of literature about the evolution of ToM in the MCI condition, which is very interesting insofar as the evolution of MCI is not yet fully understood. In fact, the conversion rate of aMCI to AD has been estimated to be 14–18% per year [26], which justifies the conception of MCI as an intermediate state between normal cognition and dementia. However, there is also evidence of a reversion from MCI to normal or near-normal aging [28], ranging from 4% to 15% in clinic-based studies and 29% to 55% in population-based studies. The complexity of the evolution of MCI condition opens stimulating questions about the evolution of ToM ability as well. Against this background, we present two single case-studies, which can be defined under a certain sense “extreme” cases of the MCI condition: a 75-year-old man, with six years of education, who converted to AD within the following five years, and a 60-year-old woman, with five years of education, who reverted to near-

normal aging within the following five years. We do not intend to compare the two cases directly, but rather to follow their evolution under their neuropsychological profile (NPS) and ToM comparing them to control groups adequate for their clinical condition.

Case Reports

Case 1

Mr. Rossi (pseudonym), a 75-year-old right-handed male at time of initial referral, with six years of education, came to the Service of Neurology of the Don Carlo Gnocchi Foundation in Milan. He presented with a history of cognitive dysfunctions, namely some evidences of forgetfulness in everyday life. However, he was independent and competent in his own self-care and in everyday activities. There was no family history of dementia. Neurological examination revealed no significant abnormalities. After neuropsychological testing, brain imaging and blood tests he received a diagnosis of MCI and Mr. Rossi underwent yearly control assessments. A remarkable decrease in amnesic functions was documented in the following five years. Moreover, the daughter reported some behavioral changes of clinical interest, such as mood deflection, significant traits of anxiety, light apathy, and sleeping disturbances. The clinical picture was recently updated as dementia (AD).

Case 2

Mrs. Bianchi (pseudonym), a 60-year-old right-handed woman was referred to the Service of Neurology of the Don Carlo Gnocchi Foundation by her general practitioner for evaluation of memory problems. Mrs Bianchi reported that she had difficulty in recalling events and concentrating. Examination revealed a bright and well-groomed woman who spoke rapidly, independent and competent in her own self-care of most everyday activities. There was no family history of dementia. Behavior was appropriate except for traits of anxiety. Basic neurologic examination was normal. After neuropsychological testing, brain imaging and blood tests she received a diagnosis of MCI and Mrs. Bianchi underwent yearly control assessments. A remarkable improvement in memory functions and behavior was documented in the following five years. The clinical picture was consistent with a reversion from MCI to near-normal aging.

Methods and Procedure

Mr. Rossi and Mrs. Bianchi were included in a research protocol on Theory of Mind in MCI [22], and were monitored for the following five years with classical NPS assessment as well as with a ToM assessment. They also underwent a structural MRI examination to follow the evolution of their clinical picture also under the neural profile. The criteria for inclusion/exclusion were the presence of a diagnosis of MCI.

Following Shanks and colleagues [29], the performance of Mr. Rossi on NPS and ToM battery tasks were compared at

time 1 (T1) to those of a group of healthy controls (N = 15, female = 11) comparable for age (mean = 73.53, SD = 3.04) and education (mean = 7.47, SD = 2.42). Control group participants were screened for vascular risk factors and excluded if they had history of head injury, of neurological or psychiatric disorders. Having converted to AD, the performances of Mr. Rossi on NPS and ToM battery tasks were then compared at time 2 (T2) to those of a group of AD patients (N = 10, female = 7) matched for age (mean = 78.00 SD = 4) and education (mean = 8.00 SD = 3). Mr. Rossi performances were statistically compared with the means of the two groups using a computerized version (<http://www.abdn.ac.uk/~psy086/dept/psychom.htm#conflims>) of the Sokal and Rolph [30] modified t test.

The performances of Mrs. Bianchi on standard NPS ToM battery tasks were compared at T1 to those of a group of healthy controls (N = 15, female = 11) comparable for age (mean = 66.93, SD = 6.91) and education (mean = 10.87, SD = 3.54). Control group participants were screened for vascular risk factors and excluded if they had history of head injury, of neurological or psychiatric disorders. Having not converted to AD, but rather reverted to near-normal cognition, the performance of Mrs. Bianchi on standard NPS and ToM battery tasks were then compared at T2 to those of a group of MCI patients (N = 7, female = 5) matched for age (mean = 69.00 SD = 4.72) and education (mean = 10.00 SD = 4.83). Mrs. Bianchi performances were statistically compared with the means of the two groups using a computerized version (<http://www.abdn.ac.uk/~psy086/dept/psychom.htm#conflims>) of the Sokal and Rolph [30] modified t test.

The comparison of the individual performance to that of the healthy control group and of the AD group and MCI group (for Case 1 and Case 2, respectively) should allow for the appreciation of the changes in their cognitive and socio-cognitive profile over time.

The study conformed to the ethical principles of the Helsinki Declaration, and informed written consent was obtained from all the included subjects before study initiation. Participants had the possibility to ask further information during the study, as well as to give up their participation at any time. The clinical

control samples were recruited at the Service of Neurology of the Don Carlo Gnocchi Foundation in Milan, who has in charge these patients. The healthy control groups were the caregivers of the patients, or volunteers doing their activity at the Don Carlo Gnocchi Foundation.

Case 1

Neuropsychological assessment

The general cognitive level was assessed using the MMSE [31], a short test of global cognitive functioning. Short term memory was evaluated through the Corsi-Span [32] and the digit span forward/backward [33]. Long term memory was assessed through the delayed recall of Rey's complex figure task [34], and the test of Prose Memory (The Short Tale Test) [35]. Linguistic abilities were assessed with the Naming task and the Token Test [36]. Executive functions were tested with the Phonemic Fluencies and the Semantic Fluencies [35], the Coloured Progressive Matrices (CPM), Raven, series A, Ab, B [37,38] and the Attentive Matrices [39].

The MMSE provided a first evidence of Mr. Rossi's cognitive decline, decreasing from 27.7 at T1 to 18.4 at T2. So, Mr. Rossi's performance in the MMSE decreased under the cutoff of normal population, resulting to be significantly different from the MMSE mean value of the healthy control group (mean = 26.83, SD = 2.35) ($t = -3.47, p < 0.01$, two tailed) and not significantly different from the MMSE value of the AD group. This result constitutes a first evidence of Mr. Rossi being an MCI converter to AD.

As **Table 1** shows, Mr. Rossi's performance on memory tasks reveals that short-term memory was not compromised, whereas a progressive decay of long-term memory was found, as his performances were not significantly different from those of the AD group. As for linguistic abilities, a decline in oral comprehension emerged. Finally, a reduction in frontal functions became evident: the performances to the Phonemic and the Semantic Fluencies were initially significantly better than those of the AD group, but then this difference disappeared.

Table 1 NPS assessment scores for Mr. Rossi compared to the AD control group.

NPS Assessment		Case 1		AD Group			
Tasks	Cut-Off	Mr. Rossi T1	Mr. Rossi T2	Mean	SD	t-value	p-value
Mmse	24	27.7	18.4	22.05	1.89	-1.4	NS
Corsi-Span	3.75	4	4.25	4.23	0.56	0.03	NS
Digit Span Forward	3.75	4.5	4.5	5.15	0.92	-0.67	NS
Digit Span Backward		3	4	3.4	0.7	-0.82	NS
Delayed Recall Complex Rey's Figure Task	9.47	10	8	5.44	5.06	0.67	NS
Prose Memory (The Short Tale Test)	8	10.5	1.25	4.5	2.29	1.25	NS
Naming Test		38	38	30.4	3.1	2.34	0.04

Token Test	26.5	27.5	23.5	31.68	2.3	-3.39	0.008
Phonemic Fluencies	17	36	27	26.5	4.88	0.1	NS
Semantic Fluencies	25	36	29	27.1	4.61	0.39	NS
Raven's Coloured Progressive Matrices	18	28.5	32.5	26.35	6.93	0.85	NS
Attentive Matrices	31	50.25	48.75	41.23	8.8	0.82	NS

Overall, Mr. Rossi's performance on the NPS battery, across the five years of follow-up, shows the typical pattern of conversion from the MCI condition to the AD condition. Specifically, there was a notable decline in general cognitive functioning, long-term memory, language understanding and frontal functions.

Theory of mind assessment

Theory of Mind ability was assessed with a paper-pencil battery of tasks specifically devised for research on adult and elderly subjects [12,18,22]. The battery taps various levels of Theory of Mind reasoning following the developmental pattern of Theory of Mind acquisition, in order to verify the consistence of such steps in the tested subjects.

A precursor of Theory of mind was assessed with the Eyes Direction Detection (EDD) task [40]. The participant observes a face with four objects around it and judges the face's preference referring to its eye-gaze direction.

The first level of false belief reasoning was assessed with the classic Deceptive box task [41]. The participant is shown a closed box, whose content has been substituted without his/her knowledge and s/he is asked to say what it contains; then the box is opened, the real content is shown and the box is closed again. The participant is asked to predict what another person would say if shown the closed box.

The second level of false belief reasoning was evaluated with the Look- and Say-prediction tasks [42-44]. The

participant has to predict the place where a character of the story thinks that another character would look for a hidden object (look-prediction) and what a character thinks that the other character would say about a hidden object (say-prediction).

Finally, a more advanced level of Theory of Mind reasoning was assessed with a selection of items from the Eyes Test [45] and stories from the Strange Stories [46,47]. Items from the Eyes Test were divided in epistemic and emotive items according to their content, as described in Castelli et al. [12] and their corresponding items of the Gender Test were used as well. Four Strange Stories, dealing with different aspects of ToM reasoning, were selected (the bluff, the manipulation of feelings, the white lie and the misunderstanding of intentions). Similarly, four Physical Stories were used as control stories (the army battle, the broken leg, the lost glasses and the multi-pack of light bulbs).

The whole battery was administered individually; answers were audio-recorded and then coded once the session was closed. For a more exhaustive description of the battery, please refer to Castelli et al. [12].

Table 2 shows a comparison between Mr. Rossi's results from the ToM battery at T1, with the mean performances of the healthy control group, and at T2 with those of the AD group.

Table 2 ToM assessment scores for Mr. Rossi compared to the healthy control group and to the AD control group.

ToM Assessment	Case 1 – T1					Case 1 – T2				
	Mean healthy controls	SD healthy controls	Mr. Rossi	t-value	p-value	Mean group AD	SD AD group	Mr. Rossi	t-value	p-value
EDD	24.33	1.76	25	0.369	NS	18.9	6.35	24	0.766	NS
Deceptive Box Task	5	0	5	-	-	4.8	0.42	5	0	NS
Look-Prediction	3.73	1.28	4	0.204	NS	1.8	0.79	1	-0.966	NS
Say-Prediction	2.53	1.13	2	-0.454	NS	1.7	0.95	2	0.301	NS
Eyes Test	9.67	2.77	9	-0.234	NS	8	2.62	6	-0.728	NS
Gender Test	14.53	1.13	14	-0.454	NS	14.3	1.95	15	0.342	NS
Emotional Items	4.47	2.1	5	0.244	NS	3.8	1.87	2	-0.918	NS

Epistemic Items	5.2	1.7	4	-0.683	NS	4.2	1.87	4	-0.102	NS
Strange Stories	5.4	1.96	2	-1.68	0.058	3.8	1.75	1	-1.526	NS
Physical Stories	6.4	1.06	7	0.548	NS	5.5	1.51	1	-2.841	0.01

Mr. Rossi performed significantly worse than the healthy control group in the Strange Stories, an ecological advanced task of Theory of Mind, and in the Physical Stories, the correspondent control task. The first result is in line with evidence showing that advanced skills of social cognition are usually the first to degenerate in people with MCI [22]. The second can be interpreted by referring to Mr. Rossi's decline in language comprehension, as shown by his poor performance on the token task.

The MMSE provided the first evidence of the preservation of Mrs. Bianchi's cognitive functioning: it not only remained above the cutoff, but also it was not significantly different from the mean MMSE value of the healthy control group (mean = 27.41, SD = 1.67) and of the MCI group at T2 (**Table 3**). This result constitutes a first evidence of Mrs. Bianchi not being an MCI converter to AD.

Case 2

Neuropsychological assessment

Mrs. Bianchi underwent the same NPS assessment of Mr. Rossi.

Table 3 NPS assessment scores for Mrs. Bianchi compared to the MCI control group.

NPS Assessment	Cut-off	Case 2		MCI Group		t-value	p-value
		Mrs. Bianchi T1	Mrs. Bianchi T2	Mean	SD		
MMSE	24	27.74	26.27	24.66	0.65	2.32	NS
Corsi-Span	3.75	5	4.25	4.14	1.06	0.66	NS
Digit Span Forward	3.75	4.5	5.5	4.79	0.85	0.78	NS
Digit Span Backward		4	3	3	1.15	0	NS
Delayed Recall Complex Rey's Figure Task	9.47	8.27	13.82	9.74	6.45	1.27	NS
Prose Memory (The Short Tale Test)	8	6	13.5	11	4.68	0.5	NS
Token Test	26.5	31	31	30.46	1.26	0.4	NS
Phonemic Fluences	17	23	26	28.14	12.62	-0.16	NS
Semantic Fluences	25	32	36	29.14	7.93	0.81	NS
Raven's Coloured Progressive Matrices	18	24	28.5	25.71	6.28	0.42	NS
Attentive Matrices	31	40.25	46	38.68	9.28	0.74	NS

Regarding memory, Mrs. Bianchi's performance showed that short-term memory was not compromised, and that long term memory was not only maintained, but also improved over time (see the improvement in the prose memory task). Furthermore, no decline was found in the linguistic abilities and in executive functions. Overall, Mrs. Bianchi's performance on the NPS battery across the five years of follow-up showed a pattern of reversion from the MCI condition to a near-normal aging condition.

Theory of mind assessment

Theory of Mind ability was assessed with the same paper-pencil battery of tasks specifically devised for research on adult and elderly subjects [12,18,22].

A comparison was performed between Mrs. Bianchi's results to the ToM battery at T1, with the mean performances of the healthy control group, and at T2 with those of the MCI group, once she had reverted (**Table 4**). Compared to healthy controls, Mrs. Bianchi showed a significantly worse performance in the more complex levels of the ToM battery, namely in the Eyes Test and in the items of the Eyes Test with an epistemic content. She also demonstrated worse

performance in the Physical Stories task, which was already present at the time of the first evaluation with respect to both groups (significantly so in comparison with healthy controls).

Table 4 ToM assessment scores for Mrs. Bianchi compared to the healthy control group and to the MCI control group.

ToM Assessment	Case 2 – T1					Case 2 – T2					
	Tasks	Mean healthy controls	SD healthy controls	Mrs. Bianchi	t-value	p-value	Mean MCI group	SD MCI group	Mrs. Bianchi	t-value	p-value
EDD	25	0	25	-	-	23.57	2.44	25	-	-	NS
Deceptive Box Task	5	0	5	-	-	5	0	5	-	-	NS
Look-Prediction	4.2	0.94	4	-0.21	NS	3	1.15	5	1.63	NS	NS
Say-Prediction	3.27	1.16	2	1.06	NS	2.14	1.21	5	2.21	0.035	NS
Eyes Test	10.93	2.43	7	-1.57	NS	9.57	3.59	5	-1.19	NS	NS
Gender Test	14.73	1.44	15	0.18	NS	14.28	1.6	16	1.01	NS	NS
Emotional Items	5.33	1.5	3	-1.5	NS	4.57	2.57	3	-	-	NS
Epistemic Items	5.67	1.76	4	-0.92	NS	5	2.31	2	-1.22	NS	NS
Strange Stories	5.4	1.59	3	-0.85	NS	5	2.52	3	-	-	NS
Physical Stories	6.53	0.99	4	-2.47	0.013	6.14	1.34	5	-0.8	NS	NS

As to the MCI group, her performances are comparable to those of the MCI control group and even better in the second-order false belief reasoning (Say-Prediction task) at T2, thus supporting the evidence of a maintenance of her profile and even a reversion to near-normal aging.

Discussion

To the best of our knowledge, the present work constitutes a first attempt of evaluating the developmental changes of ToM in the clinical condition of MCI with opposite patterns of evolution, i.e., the conversion to dementia (AD) in one case, and the reversion to near-normal aging in the other. Overall, the NPS pictures at the end of the follow up of the two patients analyzed here are in line with the clinical groups of their evolution, i.e., AD for Mr. Rossi who converted towards dementia, and MCI for Mrs. Bianchi who did not convert towards dementia. In particular, the case of Mr. Rossi is representative of the typical NPS evolution to the AD condition, and is further supported by structural MRI, showing a reduction in the volume of the hippocampal structure in line with the shifting towards a clinical condition of dementia. Regarding ToM, his evolution goes in line with previous evidences of a decay of the most complex levels of ToM reasoning [18]. Also in this case, the progressive loss of Theory of Mind appears to follow the path described by Lough and Hodges [48] of the neurodevelopmental stance: in fact, the competences degrade in the opposite direction with respect to

its acquisition during childhood, as the more advanced and ecological aspects of Theory of Mind are damaged in the early stages of dementia, whereas the basic social understanding milestones remain preserved.

The case of Mrs. Bianchi is interesting as well, because this case shows the maintenance of adequate levels of ToM reasoning in a variety of tasks, ranging from the simple ones to the more complex ones. A hypothesis worth exploring more extensively regards the possible protective role of ToM abilities in avoiding the conversion from MCI to AD: Mrs. Bianchi presented an already impaired capacity in reasoning about stories with a pure physical content (the physical stories are the control task of the corresponding ToM tasks, i.e., the Strange Stories) at T1 compared to healthy controls. However, the preserved adaptive capacity to reason about mental states, demonstrated by good performances in the Strange Stories, is likely to act as a protective factor towards unsuccessful neurocognitive aging. If this hypothesis is confirmed, it would be reasonable to think that cognitive reserve – a well-known factor protecting from dementia [49,50] – may work jointly with more socio-cognitive forms of reserve, including ToM abilities.

This work has some limitations as well. First of all, two single-cases do not allow for a generalization of our findings to the clinical population. Instead, they may constitute a first step for future research which could organize a systematic follow-up of MCI patients not only under the NPS profile, but also

under ToM functioning. This line of research should contribute to a better characterization of the progressive steps of Theory of Mind decline in people with MCI who convert to AD, and in people who do not undergo such a conversion, thus enriching the still open debate about the risk factors involved in this process beyond age and education [28,51]. Furthermore, this would be in line with the new DSM-V's requirements [27] and the proposal of Adenzato and Poletti [15] to include the evaluation of ToM abilities in the standard NPS assessment, as ToM is a relevant component of the broader domain of social cognition which undergoes significant changes with aging. This proposal is even more plausible in the light of our findings about Mrs. Bianchi. A detailed analysis of ToM performance at time 1 compared with NPS assessment on one side, and control tasks on the other, would allow for a more precise and individualized description of patients. A second limitation regards the type of ToM assessment, which should become more complex in the future, including not only the evaluation of a "cognitive" mindreading ability, but also of an "affective" one, in line with the distinction proposed by Shamay-Tsoory and colleagues [52]. This should allow for a more exhaustive picture of ToM function in aging, and, in the long run, this could support the preparation of specific training aimed at supporting ToM in the condition of unsuccessful neurocognitive aging, given the interesting first attempts carried on in successful neurocognitive aging [53]. The two cases presented here may provide a useful hint for the development of tailored ToM trainings taking into account the peculiar clinical evolution of NPS and ToM abilities across MCI patients.

Acknowledgement

We wish to thank Dr. Niels Bergsland for reading and revising the manuscript.

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