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Resting-state functional brain connectivity for human mentalizing: biobehavioral mechanisms of theory of mind in multiple sclerosis

Sara Isernia,[1] Alice Pirastru,[1] Davide Massaro,[2] Marco Rovaris,[1] Antonella Marchetti,[2] and Francesca Baglio[1]

[1]IRCCS Fondazione Don Carlo Gnocchi ONLUS, Milan 20148, Italy

[2]Research Unit on Theory of Mind, Department of Psychology, Università Cattolica del Sacro Cuore, Milan 20123, Italy

Correspondence should be addressed to Alice Pirastru, Advanced Diagnostic and Rehabilitative Therapy Centre (CADiTeR), IRCCS Fondazione Don Carlo Gnocchi ONLUS, Via Capecelatro 66, Milan 20148, Italy. E-mail: apirastru@dongnocchi.it.

Abstract

Although neural hubs of mentalizing are acknowledged, the brain mechanisms underlying mentalizing deficit, characterizing different neurological conditions, are still a matter of debate. To investigate the neural underpinning of theory of mind (ToM) deficit in multiple sclerosis (MS), a region of interest (ROI)-based resting-state fMRI study was proposed. In total, 37 MS patients (23 females, mean age = 54.08 ± 11.37 years, median Expanded Disability Status Scale = 6.00) underwent an MRI and a neuro-psychosocial examination and were compared with 20 sex-age-education matched healthy subjects. A neuroanatomical ToM model was constructed deriving 11 bilateral ROIs and then between and within-functional connectivity (FCs) were assessed to test for group differences. Correlation with psychosocial scores was also investigated. Lower ToM performance was registered for MS both in cognitive and affective ToM, significantly associated with processing speed. A disconnection between limbic–paralimbic network and prefrontal execution loops was observed. A trend of aberrant intrinsic connectivity in MS within the anterior cingulate cortex (ACC) was also reported. Finally, a correlation between cognitive ToM and intrinsic FC was detected in ACC and dorsal striatum, belonging to the limbic–paralimbic network, likely explaining the behavioral deficit in MS. The results suggest that aberrant intrinsic and extrinsic connectivity constitutes a crucial neural mechanism underlying ToM deficit in MS.

Key words: theory of mind; multiple sclerosis; resting-state functional MRI; social cognition; brain connectivity; mentalizing

Introduction

Socio-cognitive abilities constitute a complex set of interconnected and interdependent processes indispensable for social interactions (Happé and Frith, 2014). Among these, theory of mind (ToM) represents a core component referring to the ability to understand others' states of mind, such as thoughts, emotions and dispositions driving behavior (Call and Tomasello, 2008). Recent ToM models represent the multi-domain nature of this social ability, by separating a cognitive component underlying the understanding of thoughts, dispositions, and motivations, from an affective part, responsible for the comprehension of emotions (Shamay-Tsoory *et al.*, 2009, 2010; Sebastian *et al.*, 2012). The achievement of ToM skills during development is fundamental, by supporting a functional and rich social life, impacting people's well being (Thomas *et al.*, 2017). In addition, the mediating role of social cognition abilities on social quality of life has been demonstrated (Hasson-Ohayon *et al.*, 2017).

A precise description of neural areas dedicated to ToM is derived from Abu-Akel and Shamay-Tsoory's model (Abu-Akel and Shamay-Tsoory, 2011). By considering neuroscientific data from studies on clinical and not clinical populations, the model depicts the main brain networks of mentalizing. Precisely, the temporal parietal junction (TPJ) consists of the first node of the network, responsible for the detection of states of mind, that in turn communicates with superior temporal sulci (STS) or precuneus and posterior cingulate cortex (PCC). Altogether, TPJ, STS, precuneus and PCC allow the representation of agency to mental states, constituting the Core ToM Network (Isernia *et al.*, 2020). These areas are linked with both limbic and paralimbic structures, the limbic–paralimbic network, in which separate areas dedicated to cognitive and affective states of mind representations are highlighted. In particular, the amygdala, ventral striatum, ventral temporal pole, and ventral anterior cingulate cortex (ACC) are involved in affective states of mind representation, whereas the dorsal striatum, dorsal temporal pole and dorsal ACC are responsible for cognitive states of mind representation. The interconnection between cognitive and affective ToM information is carried out through ACC, the key node whose dorsal and

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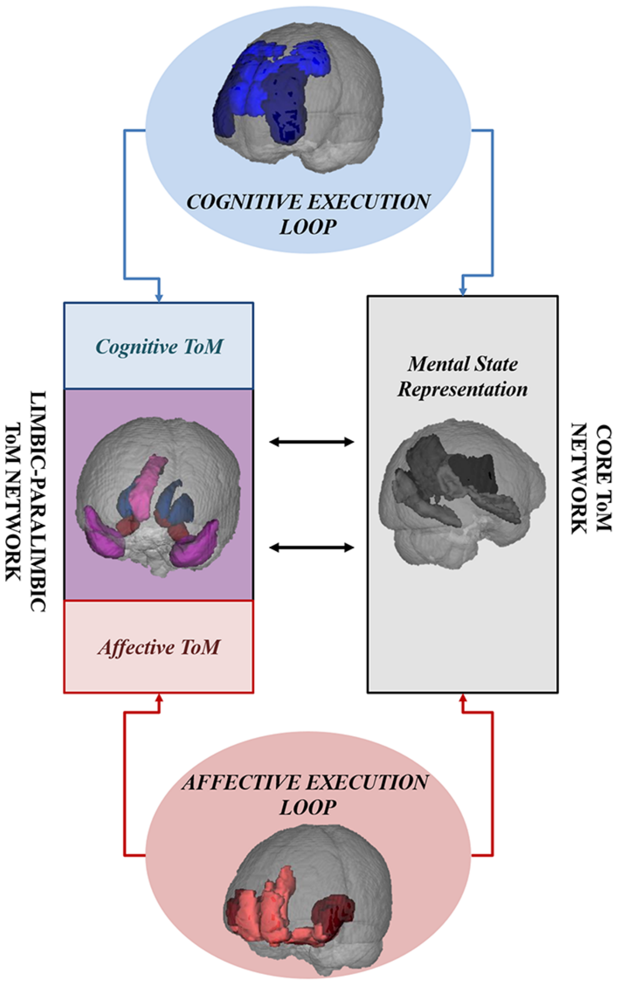


Fig. 1. Interactions existing between the ToM networks depicted in the model from Abu-Akel and Shamay-Tsoory (2011). The Core ToM network and the limbic–paralimbic network are directly linked. These two networks are connected with frontal areas through two dedicated circuits: the cognitive and affective execution loops.

ventral parts are connected and part of the cognitive and affective ToM network loop. Then, from limbic and paralimbic ToM network, information is shared with frontal areas for decision making through two dedicated circuits: the cognitive and affective execution loops. The cognitive execution loop recruits the dorsolateral and dorsomedial prefrontal cortex (PFC), whereas infero-lateral, ventro-medial PFC and orbitofrontal cortex are included in the affective execution loop (Figure 1).

Although the above-mentioned model consists of a landmark of ToM neural hub components, it is still not clear which are the brain mechanisms responsible for mentalizing deficit in pathological conditions (Elamin *et al.*, 2012; Trojsi *et al.*, 2016; Duclos *et al.*, 2018), especially related to the interaction among the separate social brain areas. More evidence-based studies are needed to investigate the cross-talk mechanisms among the different neural hubs included in the ToM brain networks likely related to the mentalizing deficit.

White matter (WM) disruption is the peculiar signature of multiple sclerosis (MS), with well-known implications on neuropsychological functions, including social cognition. MS is a condition caused by an autoimmune disease progressively destroying tissues of the central nervous system with both inflammatory and degenerative features (Schmidt, 2016). Recent contributions reported dysfunctions of ToM abilities related to the disease, revealing an aspect of MS not yet fully investigated (Chalah and Ayache, 2017). Pieces of evidence are sparse and far from a complete comprehension of this signature of the pathology. From a behavioral point of view, some works supported the presence of deficit both in cognitive and affective ToM components (Pöttgen *et al.*, 2013; Genova *et al.*, 2016; Raimo *et al.*, 2017), whereas other studies demonstrated the disruption only of cognitive but not affective ToM part (Roca *et al.*, 2014; Santangelo *et al.*, 2016; Bisecco *et al.*, 2019; Isernia *et al.*, 2019, 2020). Moreover, the possible relation between ToM deficit and cognitive difficulties in MS is still a controversial topic, with evidence supporting the direct correlation between psychosocial and neuropsychological functions (Dulau *et al.*, 2017; Ciampi *et al.*, 2018; Bisecco *et al.*, 2019; Isernia *et al.*, 2020), and some contributions demonstrating the absence of a subsisting association (Neuhaus *et al.*, 2018).

At the brain level, the underlying mechanisms related to these difficulties have been ascribed to both gray matter (GM) atrophy (Mike *et al.*, 2013; Chalah *et al.*, 2017; Batista *et al.*, 2017a; Ciampi *et al.*, 2018; Pitteri *et al.*, 2019) and WM damage (Mike *et al.*, 2013; Batista *et al.*, 2017b; Isernia *et al.*, 2020). Concerning GM, atrophy has been reported both at a global and a local level and has been related to social cognition (ToM) deficits (Ciampi *et al.*, 2018). In particular, the volume of the amygdala (Batista *et al.*, 2017a; Pitteri *et al.*, 2019) and the cingulate cortex (Chalah *et al.*, 2017) seems to play a substantial role in social cognition abilities and ToM. Conversely, regarding WM damage, a widespread microstructural disruption, leading to anatomical disconnection, has been linked to poor ToM performances (Batista *et al.*, 2017b; Isernia *et al.*, 2020). In details, a correlation was found between ToM scores and normal-appearing WM microstructural indices of corpus callosum, fornix, tapetum, uncinated fasciculus, left inferior cerebellar peduncle, and right-superior temporal gyrus (Batista *et al.*, 2017b). Similarly, in Isernia *et al.* (2020), a significant association was found between cognitive ToM and normal-appearing microstructural indices of tracts connecting key ToM GM regions. Noteworthily, this latter study focused on specific GM areas, depicted in Abu-Akel and Shamay-Tsoory's ToM model (Abu-Akel and Shamay-Tsoory, 2011) and their anatomical connections to explore brain correlates implied in ToM abilities of MS with an a-priori hypothesis (Isernia *et al.*, 2020). The latest contributions investigated ToM difficulties in MS by studying blood oxygen level dependent signal as an indirect measure of neural activation at rest (Bisecco *et al.*, 2019; Golde *et al.*, 2020; Labbe *et al.*, 2020). Resting state functional MRI is a suitable technique for capturing both disease-driven modification, in terms of functional reorganization, and its link to clinical variables (Hawellek *et al.*, 2011; Bisecco *et al.*, 2019; Labbe *et al.*, 2020; Rocca *et al.*, 2020). Another advantage of this approach is that it allows to focus on the communication (i.e. functional connectivity, FC) between GM areas. By adopting an explorative perspective, Bisecco *et al.* (2019) reported a significant link between resting-state FC of the default mode network, the executive network, and the limbic network, and ToM performance in MS. Also, Labbe *et al.* (2020) revealed that ToM difficulties were linked to the connectivity of cerebellar areas and the amygdala. On the other hand, no significant relationship between resting-state FC and ToM performance was found by Golde *et al.* (2020).

The present work aims to contribute to the identification of the main brain connectivity mechanisms responsible for

ToM efficiency, by adopting a neuro-clinical approach, and investigates the efficacy of the cross-talk among different social neural hubs in MS. In detail, by proposing a resting-state fMRI study with a theory-driven approach, we focused on regions of interest (ROIs) dedicated to ToM processes (Abu-Akel and Shamay-Tsoory, 2011) to explore the role of the between and within connectivity inside the ToM networks on mentalizing capability. In these terms, our twofold aim is as follows: (i) to study the efficiency of between connectivity among the ToM brain hubs on social cognition abilities and (ii) to study the efficiency of within connectivity inside the ToM brain network components. Specifically, we expect to find a functional disconnection between specific areas of the ToM networks, such as the limbic–paralimbic and the core ToM network, and cognitive execution brain areas explaining ToM performance in MS, as suggested by previous work (Isernia *et al.*, 2020). Also, by investigating within connectivity, we expect to reveal MS-related changes in neural activity of single ToM areas, such as the ones characterized by reduced morphometric indexes in a previous study (Isernia *et al.*, 2020): temporal pole and dorsal and ventral striatum.

Method and materials

Participants

Fifty-seven subjects voluntarily took part in the study: 37 people with MS and 20 healthy controls (HCs).

The enrollment of the participants was carried out at the Multiple Sclerosis Centre and Rehabilitation Unit of the IRCCS Don Carlo Gnocchi Foundation of Milan (Italy).

After enrollment, MS patients were screened for study's eligibility following specific inclusion criteria: diagnosis of MS (Polman *et al.*, 2011), age <80, years of education ≥5, a stable pharmacological treatment for at least three months, absence of relapses and use of steroid treatment during the last month. Patients were considered not suitable for the enrollment whether they presented other neurological diseases different from MS, psychiatric illness, moderate-to-severe cognitive impairment, visual or hearing impairment affecting test performance, contraindications to MRI scanning, as reported in the clinical documentations.

A clinical screening was carried out by a neurologist of the clinic to collect the clinical history of the patient (disease duration, level of disability).

The enrollment of HC followed these inclusion criteria: absence of neurological or psychiatric illness, absence of cognitive impairment, no drug use affecting the performance of evaluation tests and no contraindications to MRI scanning.

Before participating in the study, subjects read and signed the written informed consent.

The study was approved by the Don Carlo Gnocchi Ethics Committee and the Università Cattolica del Sacro Cuore Ethics Committee.

Procedure

After being enrolled and screened for eligibility, participants were involved in an individual neuropsychological evaluation including a conventional neuropsychological battery, social cognition measures and behavioral assessment tools. The duration of the evaluation session lasted about 2 h for people with MS and 1 h and a half for HC (due to a reduced neuropsychological battery). Then, each subject underwent a 1.5 MRI scanning session.

Neuropsychological evaluation

To screen psycho-behavioral symptoms, two inventories evaluating the behavioral state were included in the assessment: the Beck Depression Inventory (BDI-II; Wang and Gorenstein, 2013), recording depressive states both related to physical and mental conditions (range 0–63), and the State-Trait Anxiety Inventory—Y1 (STAI-Y1, Santangelo *et al.*, 2016), detecting the clinical anxiety state (range 20–80).

To assess neuropsychological performance, all subjects were evaluated through the Montreal Cognitive Assessment (MoCA) test, as a measure of the general cognitive level. Nasreddine's correction (Nasreddine *et al.*, 2005) was considered to calculate total scores adjusted for age and education. Additionally, for a deep assessment of cognitive difficulties, the Brief Repeatable Battery of Neuropsychological Test (BRB-NT; Bever *et al.*, 1995) was administered in the MS group, comprising the following tests: the Selecting Reminding Test—Long-Term Storage, the Selective Reminding Test—Consistent Long-Term Retrieval, the 10/36 Spatial Recall Test, the Symbol Digit Modalities Test (SDMT), the Paced Auditory Serial Addition Test, the Delayed Recall of the Selective Reminding Test, the Delayed Recall of the 10/36 Spatial Recall Test and the Word List Generation.

To evaluate the ToM profile, two composite scores of cognitive and affective ToMs were calculated, the CToM and AToM, respectively, according to the procedure of Isernia *et al.* (2020), by averaging z-scores of tests and subtests separately for the cognitive and affective ToM measures:

- Strange Stories (SS; Happé, 1994): A selection of eight stories from the full version was considered for the purpose of the study. The subjects listened mental content stories and were invited to explain reasons underlying the behavior of characters. Each story was scored 0–2 following Happé's (1994) instructions (2 = correct mental state reported, 1 = factual explanation of behavior, 0 = no mental state or erroneous explanation) for a total score ranging 0–16.
- Reading the Mind in The Eyes Test (ET; Baron-Cohen *et al.*, 2001): The participants were shown static stimuli depicting black and white photographs of gazes of individuals expressing a state of mind and were invited to choose one of the four mental states reported for each item. Each item was scored 0–1 for a total score of 0–36.
- Faux Pas (FP; Baron-Cohen *et al.*, 1999): Four stories were selected from the full version of the tool for the purpose of the study. The participants listened stories in which a FP occurred and they were invited to answer six questions for each story, investigating comprehension, intentionality and emotions, understanding driving characters' behaviors. Intentionality and emotions items were considered to calculate cognitive (FP_cog) and affective (FP_aff) ToM scores, both ranging 0–4.
- Movies for the Assessment of Social Cognition (MASC; Dziobek *et al.*, 2006): A 15 min video showing social interactions in an ecological setting was presented to participants. The multimedia content was interrupted by multiple-choice questions on mental state comprehension for 42 times (items). Cognitive and affective ToM scores were obtained by summing correct responses on intentions and thoughts (0–25) and emotions (0–17), respectively.

The CToM and AToM composite scores were used to investigated associations with functional MRI examination.

MRI data acquisition

All of the enrolled subjects underwent MRI examination, and the following protocol was acquired using a 1.5T Siemens Avanto Scanner (Erlangen, Germany) equipped with a 12-channel head coil: (i) a 3D high-resolution magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted image (repetition time (TR) = 900 ms, echo time (TE) = 3.3 ms, inversion time (TI) = 1100 ms, matrix size = 192 × 256 × 176, resolution = 1 mm^3 isotropic), which was used as anatomical reference; (ii) a double-echo turbo spin echo proton-density (PD/T2)-weighted anatomical image (TR = 5550 ms, TE = 23/103 ms, matrix size = 320 × 320 × 45, resolution = 0.8 × 0.8 × 3 mm^3), which was acquired to exclude gross brain abnormalities; and (iii) a multi-echo resting-state fMRI sequence (TR = 2570 ms, TE = 15/34/54 ms, matrix size = 64 × 64 × 31, resolution = 3.75 × 3.75 × 4.5 mm^3, 200 volumes).

MRI data processing

The WM hyperintensities were segmented from the PD-weighted images by an experienced neuroradiologist with the Jim 6.0 software package (http://www.xinapse.com/) and aligned to the subjects' MPRAGE using the Advanced Normalization Tools (ANTs) (Smith, 2002; Avants *et al.*, 2011).

The MPRAGE images were first skull-stripped with the FSL brain extraction toolbox (BET; Smith, 2002), and then, the correction of the WM hyper intensities was performed using the FSL lesion filling algorithm (Battaglini *et al.*, 2012). Finally, the 'filled' MPRAGE volumes were normalized to the Montreal Neurological Institute (MNI) standard using ANTs (Avants *et al.*, 2011).

The resting-state fMRI datasets were checked for movements, and the volumes were retained only if the relative head motion, as assessed with FSL FEAT, was below 0.5 mm. The resting-state fMRI datasets were processed according to Kundu *et al.* (2012) using the ME-ICA pipeline. Specifically, the first 10 volumes were discarded to account for magnetization stabilization. After standard preprocessing (slice time correction, motion correction and re-alignment), the three echoes were combined to derive an optimal combination volume. The last step consisted of denoising based on ICA estimation and components classification, either in noise or signal components, on the basis of TE dependencies. The denoised volumes were then linearly registered to the subjects' MPRAGE using the FSL boundary-based registration (Greve and Fischl, 2009). Finally, the resting-state fMRI data were normalized to the MNI standard space using ANTs (Avants *et al.*, 2011).

To construct a neuroanatomical ToM model according to the one described in Abu-Akel and Shamay-Tsoory (2011), we derived 11 bilateral ROIs from different atlases (Destrieux *et al.*, 2010; Mars *et al.*, 2012; Sallet *et al.*, 2013; Neubert *et al.*, 2014; Tziortzi *et al.*, 2014). Specifically, we extracted bilateral ROI for TPJ, precuneus and PCC, STS (anterior division), ACC, TP, dorsal medial PFC, dorsal lateral PFC, dorsal striatum, orbito-frontal cortex and ventromedial PFC, infero-lateral PFC and ventral striatum and amygdala. For a detailed description of the model, refer to Table 1 and Figure 1.

We evaluated both between (correlation) and within (amplitude) ROI resting-state connectivity by applying the FSLnets toolbox (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets) to the subjects' time series extracted from the selected ROI using the FSL dual regression algorithm (Beckmann *et al.*, 2009).

To measure the between ROI connectivity, we derived full-correlation matrices computing the Pearson's correlation coefficients between all pairs of ROIs that were then converted to z-scores. The within connectivity, namely, the amplitude, was measured as the temporal standard deviation of the time series of the BOLD fluctuations.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics software (Version 24) and FSL Randomise tool (Winkler *et al.*, 2014).

The Kolmogorov–Smirnov test was run to test the normality distribution of variables, and parametric or non-parametric tests were utilized accordingly.

To verify that MS and HC groups were balanced for demographical variables, the chi-squared test, the Mann–Whitney test and an independent *t*-test (accounting for homogeneity of variance) were performed. Means, frequencies and standard deviations were also calculated to describe sample characteristics.

(1) To test differences between groups (HC *vs* MS) in mentalizing performance, a univariate GLM test was performed.
(2) To investigate the relation between ToM performance and neuropsychological level, partial correlations were run in the MS group.
(3) The group comparison and correlation analyses with CToM and AToM scores were obtained by means of the FSL Randomise tool (Winkler *et al.*, 2014), embedded in FSLNets, for the between connectivity matrices using GLM. The results were corrected for multiple comparisons with family wise error (FWE) correction (to avoid the risk of type I errors) and considered significant if $p_{FWE} \leq .05$.

Regarding the within connectivity, further statistical analyses were performed with SPSS only for the ROI showing group differences in between connectivity. The group comparison was performed using a GLM. Partial correlations were performed between the ROI amplitude and CToM and AToM scores. The correction for multiple comparison was performed using the false discovery rate (FDR) (to avoid the risk of type II errors), and results were considered significant if $p_{FDR} \leq .05$.

All analyses considered sex, age and education level as covariates inside statistical models.

Results

Participants and neurocognitive profiles

Fifty-seven participants were enrolled: 20 HC and 37 MS. In total, 59% of MS was under immunomodulatory or immunosuppressive treatment with fingolimod (15%), interferon beta (15%), glatiramer acetate (40%), dimetilfumarate or natalizumab (20%), ciclofosfamide (5%) and teriflunomide (5%).

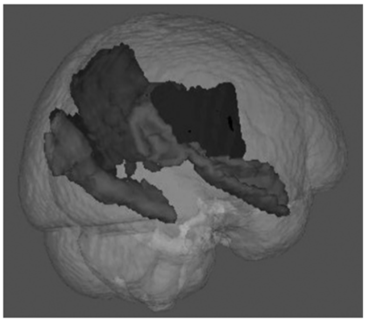
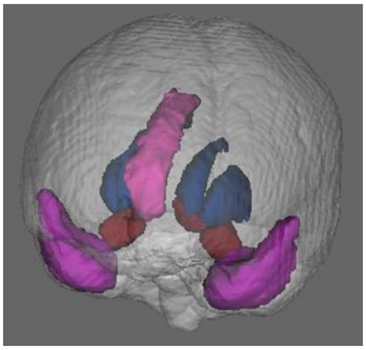
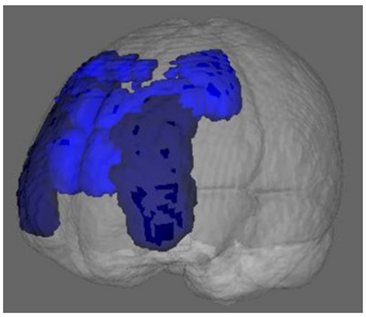
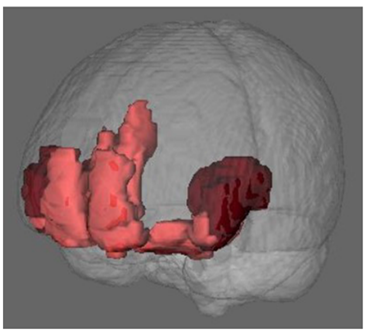
Table 2 reports the demographic, psycho-behavioral, neuropsychological and social cognition profile of the sample.

The two groups (MS *vs* HC) were balanced for sex, age and educational level.

Regarding the psycho-behavioral profile, more depressive related symptoms were registered in the BDI-II scale in MS than HC, considering both the total score ($P = 0.001$, $\eta^2 = 0.144$, $\omega = 0.848$) and sub-scores (somatic symptoms: $P = 0.007$, $\eta^2 = 0.126$, $\omega = 0.789$; cognitive symptoms: $P = 0.001$, $\eta^2 = 0.124$, $\omega = 0.782$), with a level of depression within the minimal depression range.

At the neuropsychological level, the comparison between the two groups highlighted a higher performance of HC than MS in the global cognitive level (MoCA score: $P = 0.027$, $\eta^2 = 0.101$, $\omega = 0.683$). Additionally, the BRB-NT battery demonstrated

Table 1. ToM model ROIs

ROI	ToM networks and functions	Atlas
	'Core' ToM network:	
	TPJ	Mars TPJ Parcellation
	STS (anterior division)	Destrieux Atlas
	PCC and precuneus	Harvard-Oxford Cortical Atlas
	Limbic–paralimbic ToM network:	
	ACC	Harvard-Oxford Cortical Atlas
	Temporal pole	Harvard-Oxford Cortical Atlas
	Dorsal striatum	Striatum Structural Atlas
	Ventral striatum/amygdala	Striatum Structural Atlas/Harvard-Oxford Subcortical Atlas
	Cognitive execution loop:	
	Dorsolateral PFC	Sallet Dorsal-Frontal Parcellation
	Dorsomedial PFC	Sallet Dorsal-Frontal Parcellation
	Affective execution loop:	
	Inferolateral PFC	Neubert Ventral-Frontal Parcellation
	OFC/ventromedial PFC	Neubert Ventral-Frontal Parcellation/Neubert Cingulate Orbito-Frontal Parcellation

The main ToM networks and their sub-divisions defined accordingly to Abu-Akel and Shamay-Tsoory (2011) are reported in the table, together with the atlas used for their derivation. ROI = regions of interest; ToM = theory of mind; TPJ = temporo-parietal junction; STS = superior temporal sulcus; PCC = posterior cingulate cortex; ACC = anterior temporal cortex; PFC = prefrontal cortex; OFC = orbitofrontal cortex.

a generally preserved level of attention, speed processing, verbal fluency and immediate and delayed memory in MS, according to the normative values and cut-off scores (Bever *et al.*, 1995).

Concerning the ToM profile, we found group differences both in cognitive ToM (SS: $P < 0.001$, $\eta^2 = 0.245$, $\omega = 0.981$; FP_cog: $p = 0.007$, $\eta^2 = 0.131$, $\omega = 0.785$; MASC_cog: $P = 0.001$, $\eta^2 = 0.195$, $\omega = 0.937$) and affective ToM (ET: $P = 0.002$, $\eta^2 = 0.175$, $\omega = 0.903$;

Table 2. Characteristic of the sample

	HC	MS	Test-value	P-value
N	20	37		
Demographics				
Sex (Ma:F)	10:10	14:23	0.788[a]	0.375
Age (M, sd)	53.80, 9.92	54.08, 11.37	0.093[b]	0.926
Education (y) (M, sd)	13.35, 3.15	12.11, 3.79	1.249[b]	0.217
MS phenotype (RR:Pr)	–	20:17	–	
Disease duration (y) (M, sd)	–	15.46, 9.85	–	
EDSS (median, IR)	–	6.00, 2.25	–	
Psycho-behavioral profile				
BDI-II (M, sd)	3.85, 4.72	9.65, 7.77	172.00[c]	0.001
Somatic symptoms	3.20, 3.82	6.78, 4.95	2.812[b]	0.007
Cognitive symptoms	0.65, 1.31	2.86, 3.41	184.50[c]	0.001
STAY-I (M, sd)	44.40, 3.56	41.22, 4.07	274.50[c]	0.107
Neuropsychological profile				
MoCA (M, sd)	26.55, 1.82	24.62, 3.20	239.00[c]	0.027
BRB-NT (M, sd)				
Selective Reminding Test—Long-Term Storage	–	39.31, 12.96	–	
Selective Reminding Test—Consistent Long-Term Retrieval	–	33.24, 15.11	–	
10/36 Spatial Recall	–	20.71, 5.49	–	
Symbol Digiy Modalities	–	44.83, 14.50	–	
Paced Auditory Serial Addition 3	–	38.50, 11.60	–	
Paced Auditory Serial Addition 2	–	30.15, 9.41	–	
Delayed Recall of the Selective Reminding	–	6.99, 2.44	–	
Delayed Recall of the 10/36 Spatial Recall	–	7.01, 2.37	–	
Word List Generation	–	21.57, 5.77	–	
Theory of Mind profile				
SS (M, sd)	0.60, 0.73	−0.29, 0.99	16.916[d]	<0.001
FP_cog (M, sd)	0.96, 0.91	0.18, 0.96	7.856[d]	0.007
FP_aff (M, sd)	0.09, 0.93	−0.06, 1.06	0.147[d]	0.703
ET (M, sd)	0.58, 1.00	−0.46, 1.29	11.046[d]	0.002
MASC_cog (M, sd)	0.53, 0.52	−0.31, 0.97	12.64[d]	0.001
MASC_aff (M, sd)	0.48, 0.82	−0.28, 0.89	9.151[d]	0.004
CToM (M, sd)	0.70, 0.43	−0.14, 0.75	22.951[d]	<0.001
AToM (M, sd)	0.38, 0.51	0.27, 0.76	11.337[d]	0.001

[a]Chi-squared;
[b]independent *t*-test;
[c]Mann–Whitney test;
[d]GLM analysis. $P < 0.05$ is reported in bold.
Ma = males; F = females; M = mean; sd = standard deviation; y = years; IR = interquartile range; HC = healthy control; MS = multiple sclerosis; RR = relapsing–remitting; Pr = progressive; EDSS = Extended Disability Status Scale; BDI-II = Beck Depression Inventory; STAY-I = State-Trait Anxiety Inventory—Y1; MoCA = Montreal Cognitive Assessment; BRB-NT = Brief Repeatable Battery of Neuropsychological Test; SS = Strange Stories; FP_cog = cognitive items of Faux Pas; FP_aff = affective items of Faux Pas; ET = Reading the Mind in the Eyes test; MASC_cog = Cognitive items of Movie for Assessment of Social Cognition; MASC_aff = Affective items of Movie for Assessment of Social Cognition; CToM = cognitive theory of mind; AToM = affective theory of mind.

MASC_aff: $P = 0.004$, $\eta^2 = 0.150$, $\omega = 0.843$). Finally, ToM measures showed a statistically significant difference between groups in both cognitive and affective ToMs (CToM: $P < 0.001$, $\eta^2 = 0.306$, $\omega = 0.997$; AToM: $P = 0.001$, $\eta^2 = 0.179$, $\omega = 0.911$). These results survived also after controlling for BDI and MoCA variables (CToM: $P = 0.002$, $\eta^2 = 0.183$, $\omega = 0.907$; AToM: $P = 0.006$, $\eta^2 = 0.140$, $\omega = 0.799$).

Partial correlations between composite scores of ToM and neuropsychological and behavioral variables showed a statistically significant correlation between MoCA and CToM ($rho = 0.433$, $P < 0.001$) and between SDMT and both CToM ($rho = 0.526$, $P = 0.002$) and AToM ($r = 0.389$, $P = 0.025$).

MRI assessment

The group comparison revealed a higher resting-state FC for HC with respect to MS both between dorsal striatum and dorsolateral PFC ($p_{FWE} = 0.043$, z-values' HC mean $= 4.6 \pm 2.5$, z-values' MS mean $= 2.5 \pm 2.3$) and between ACC and orbital and ventromedial PFC ($p_{FWE} = 0.05$, z-values' HC mean $= 5.7 \pm 3.9$, z-values' MS mean $= 3.9 \pm 2.4$), Figure 2.

No significant correlations were found with CToM and AToM scores.

No significant results were found when comparing the amplitude values between the two groups, although a trend ($p_{uncorr} = 0.029$) was detected in terms of amplitude reduction in ACC for SM (z-values' mean $= 10.6 \pm 2.5$) with respect to HC (z-values' mean $= 12.6 \pm 4.2$). Significant partial correlations were found instead between CToM scores and amplitude values in both dorsal striatum ($r = 0.461$, $p_{FDR} = 0.024$) and ACC ($r = 0.462$, $p_{FDR} = 0.024$) for the MS group. These correlations were confirmed also controlling for MoCA (dorsal striatum and CToM: $r = 483$, $p_{FDR} = 0.016$; ACC and CToM: $r = 0.406$, $p_{FDR} = 0.038$).

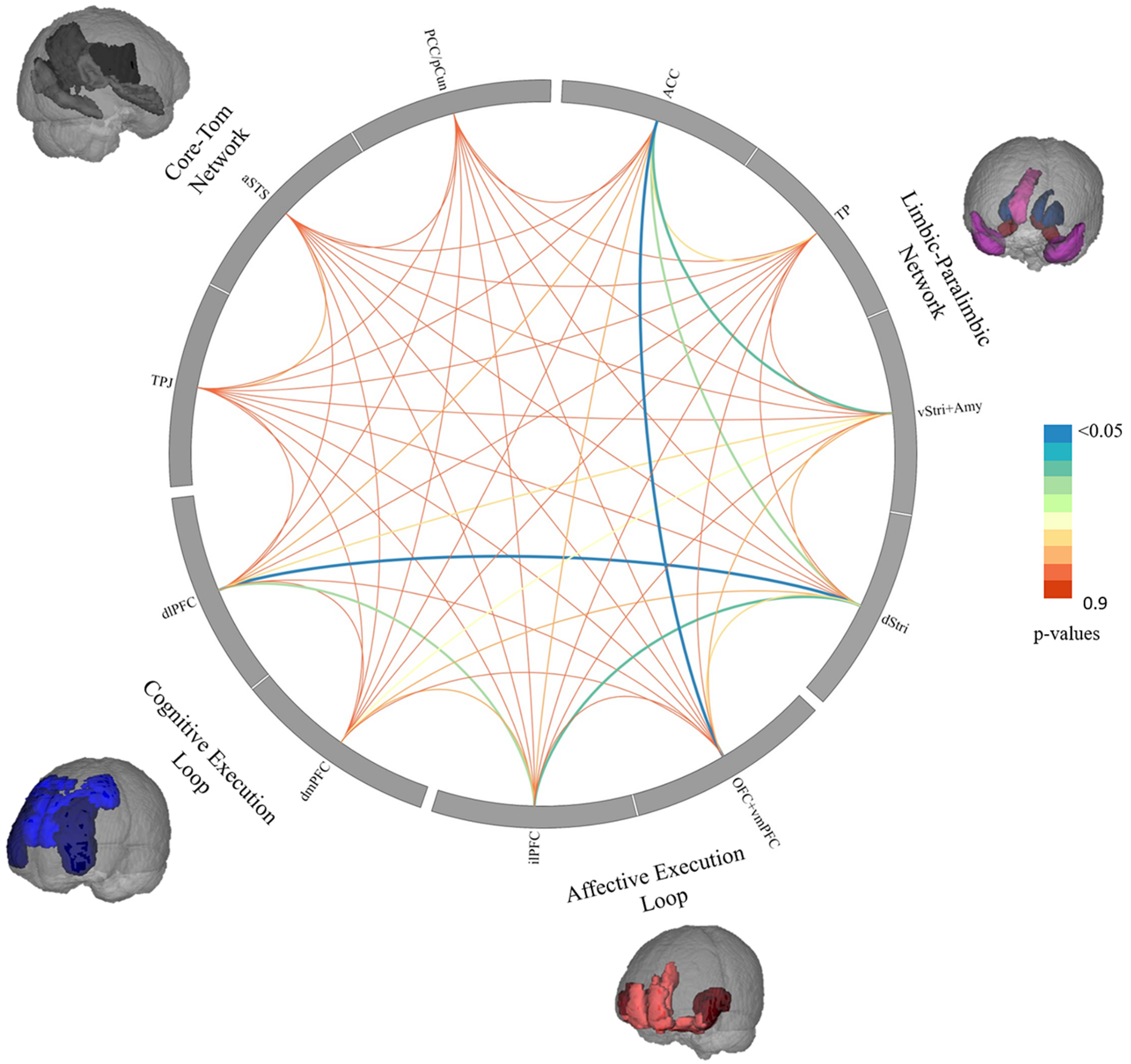


Fig. 2. FWE-corrected *P*-values obtained from the group comparison of the functional connectivity between all of the pairs of ROIs included in the model, in a circular representation. Statistically significant results (links, $P < 0.05$) are highlighted in blue according to the colorbar. ACC = anterior cingulate cortex; TP = temporal pole; vStri + Amy = ventral Striatum and amygdala; dStri = dorsal striatum; OFC + vmPFC = orbitofrontal cortex and ventromedial prefrontal cortex; ilPFC = inferolateral prefrontal cortex; dmPFC = dorsal medial prefrontal cortex; dlPFC = dorsal lateral prefrontal cortex; TPJ = temporo-parietal junction; aSTS = superior temporal sulcus (anterior portion); PCC/pCun = posterior cingulate cortex and precuneus.

Discussion

The present study aimed to investigate the role of connectivity brain mechanisms in the complex ToM circuit by investigating neural underpinnings responsible for mentalizing difficulties in MS subjects expected to have a ToM deficit. Especially, the ToM neural network model of Abu-Akel and Shamay-Tsoory (2011) has been considered to define the brain regions consisting of essential ToM neural hubs, looking at both cognitive and affective ToM correlates. Specifically, two main brain networks were identified as responsible for the efficiency of mentalizing capabilities, the Core ToM network and the limbic–paralimbic network. In addition, ToM abilities are known to rely on two ancillary networks, involving medial and lateral frontal areas, indispensable for affective and cognitive action execution and planning (Table 1 and Figure 1).

In this work, we evaluated the efficiency of network connectivity by focusing on each component of the above-mentioned ToM model both in terms of (i) between connectivity and (ii) within connectivity. First, we investigated the efficiency of communication between ToM neural hubs. Then, we measured the amplitude of the activation within each separate ToM brain area included in the model.

Considering the communication among different ToM hubs, in line with our hypothesis and previous work (Isernia *et al.*, 2020), we detected reduced FC between two specific networks of the Abu-Akel and Shamay-Tsoory (2011) model in our clinical sample: the limbic–paralimbic network and execution prefrontal cortices. Especially, this pattern of reduced brain activation was observed in both affective and cognitive ToM pathways. In fact, we found a decreased FC at rest in MS between the ACC and the orbital/ventromedial PFC and between the dorsal striatum and the dorsolateral PFC. As described in the Abu-Akel and Shamay-Tsoory (2011) model, the interconnection between limbic cortical and sub-cortical areas and neocortex subserves the execution and application nodes of mentalizing by assuring the utilization of the states of mind representation for the decision-making and the action planning. Within the prefrontal areas, the dorsolateral PFC is indicated as the key cognitive execution structure, inside the cognitive execution loop, while the inferolateral PFC represents its analogous for the affective execution loop. Interestingly, in our study, the damage observed in the connectivity seemed to involve the key node of the cognitive execution ToM, with a consistent impairment in the cognitive ToM pathway. Instead, concerning the affective execution loop, only communication with ventral streams of PFC, but not inferolateral PFC, appeared to be affected. Previous work (Weygandt *et al.*, 2019) revealed that the reduced GM volume of striatum and diffusion complexity in PFC is associated with decision-making difficulties in MS. The fact that the FC damage was limited to the communication between ToM networks and execution loops leads to assuming the presence of a specific deficit in the action planning derived from states of mind representation and not only in the generation of mental states attributions. On the other hand, this damage could affect the ancillary role of high-order cognitive functions on ToM. This result is supported by the link between the measure of attention and information processing speed (SDMT) and both cognitive and affective ToMs in our MS sample. The link between these two aspects of cognition is not unexpected. In fact, the impairment of these latter functions is recognized already at the early stages of the disease (Brochet and Ruet, 2019), as well as the ToM difficulties (Raimo *et al.*, 2017). Accordingly, Bisecco *et al.* (2019) revealed our same finding in a sample of relapsing–remitting MS. Moreover, Dulau *et al.* (2017) demonstrated that about 50% of ToM performance in MS is explained by the presence of cognitive impairment, remarking the role of the cognitive deficit in mentalizing in this clinical population.

Moving to the within connectivity of ToM neural components, we partially confirmed our hypotheses. In fact, we registered an alteration inside the limbic–paralimbic network in the clinical population, indicating the central role of the specific circuit in the processing of cognitive and affective mentalizing information. However, the registered impairment did not affect all of the expected ToM hubs, as previously revealed (Isernia *et al.*, 2020). Specifically, we observed a trend of reduced activation amplitude of ACC in MS with respect to HC. This is in line with the findings of Bisecco *et al.* (2019), who reported a decreased resting-state FC in the cingulate gyrus for MS patients. Interestingly, a positive correlation between the intrinsic connectivity of ACC, belonging to the limbic–paralimbic network, and cognitive ToM in the clinical group was found. Moreover, in the same network, we reported a significant relation between the activation amplitude of the dorsal striatum and the cognitive ToM performance. These shreds of evidence likely suggest the role of the intrinsic connectivity within the limbic–paralimbic network as the brain mechanism related to the ToM ability in MS. Accordingly, both ACC and striatum contribute to conveying information to cortical and sub-cortical areas and are indispensable neural hubs for the complex mentalizing ability (Abu-Akel and Shamay-Tsoory, 2011). Concerning the ACC, its contribution inside the ToM neural network has been ascribed to self-reflection, as well as to a variety of cognitive functions (van der Meer *et al.*, 2010; Abu-Akel and Shamay-Tsoory, 2011) implied in processes for action planning and responses. Also, the central role of the striatum as the neural basis of ToM has been detailed in previous studies, with its dorsal part recruited for cognitive ToM ability (Roca *et al.*, 2010; Abu-Akel and Shamay-Tsoory, 2011; Poletti *et al.*, 2011).

Interestingly, both ACC and dorsal striatum have been related not only to social functions but also to pure neuro-cognitive abilities in MS. A decreased FC in the ACC has been detected for MS with respect to HC, which is more evident in patients with reduced cognitive abilities (Roca *et al.*, 2010). In particular, the ACC has been proven to be strongly implicated in the cognitive impairment of MS patients (Roca *et al.*, 2010). In fact, besides typical social cognition processes, ACC is especially involved in response selection, working memory, cognitive control and attentional shifting (Leber *et al.*, 2008; Abu-Akel and Shamay-Tsoory, 2011). Also, activation of ACC at rest has been studied with a seed-based approach to evaluate the functional substrates of the cognitive rehabilitation efficacy. Specifically, increased connectivity between ACC and parietal and frontal areas was found in MS patients after cognitive rehabilitation associated with significantly higher performance in neuropsychological measures (Filippi *et al.*, 2012; Parisi *et al.*, 2012). Regarding the striatum, Cavallari *et al.* (2014) revealed an association between fractional anisotropy in its dorsal portion and cognitive neuropsychological measures. Finally, Chalah and Ayache (2020) indicated the role of striatum in the integration of social information.

Overall, our results likely suggest a subsisting overlap between psycho-social and cognitive neural network integrity by explaining the ToM performance in MS in terms of the level of the within connectivity pattern of two structures with a central role in cognitive processes. This relation has also been supported in a previous contribution (Bisecco *et al.*, 2019). In line with this evidence, different studies propose an executive accounts perspective (Wade *et al.*, 2018) postulating that cognitive ToM impairment partly grounds on difficulties in inhibition and working memory, consisting in the inefficiency in differentiating between own–other mental states and holding significant information of the context (Carlson *et al.*, 2015).

Altogether our results consisted of a preliminary finding in favor of the bio-behavioral link between cognitive and social processes, and the implication of purely cognitive deficits on social cognitive impairment has to be further investigated, especially with a focus on its neural substrates in a longitudinal perspective. Indeed, a significant insight derives from a longitudinal study in a group of patients with mild cognitive impairment (Rossetto *et al.*, 2020), which demonstrated the association between cognitive ToM performance and changes in the level of cognitive function after rehabilitation, confirming the intrinsic relationship subsisting between ToM limbic–paralimbic and execution loop networks and suggesting the beneficial effect of cross-talk between the specific and supportive ToM circuits.

The present study is not without limitations. First, in our model, it was not possible to differentiate the dorsal and ventral subdivisions of both ACC and TP that are separately implicated in cognitive and affective ToM processing. This aspect might have prevented us to find a correlation with affective ToM scores. Furthermore, a 1.5T field scanner was used for the acquisition, which entails a relatively limited signal-to-noise ratio (SNR). However, the resting-state fMRI sequence was optimized to both improve SNR and reduce image distortion caused by susceptibility artifacts, thanks to the use of multi-echo acquisition.

Conclusion

Overall, our results indicated the presence of damage in the intrinsic connectivity of the limbic–paralimbic network, which showed an additional impairment in the communication efficiency with the two ancillary execution loops. In particular, the dorsal striatum and the ACC might represent crucial hubs underlying ToM abilities in MS. Given the established role of these neural structures in cognitive processes, our study suggests that ToM deficit in MS could be linked to the disease-related damage of neural hub overlapping psycho-social and cognitive networks.

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Conflict of interest

The authors declare no competing financial interests.

Authors' contributions

A.M., D.M., F.B. and S.I. conceived the study; A.P. and S.I. performed formal analysis; S.I. and M.R. enrolled participants and carried out the behavioral evaluation; A.P., F.B. and S.I. interpreted the results; S.I. and A.P. wrote the first draft of the manuscript. All authors reviewed, edited and approved the final version of the manuscript.

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