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Theory of Mind in Myotonic Dystrophy Type 1 Is Associated With Cortical Gyrification and White Matter Hyperintensities

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ABSTRACT

Background: Theory of Mind (ToM) Refers to the ability to infer other people's thoughts (Cognitive ToM) and emotions (Affective ToM). Myotonic Dystrophy Type 1 (DM1) Patients Showed an impairment of ToM capacities, but the underlying neural mechanisms remain poorly understood.

Methods: We included 58 adult non-congenital DM1 patients from the DMVASCOG cohort, who underwent a ToM evaluation using the Movie for the Assessment of Social Cognition and a brain MRI. Association of ToM scores with cortical thickness and gyrification was assessed using FreeSurfer software, and associations with white matter hyperintensities were assessed using SVR-LSM. Finally, we included all the significantly associated parameters in a multivariate model.

Results: The ToM total score and cognitive subscore were both associated with the local gyrification in the right superior parietal gyrus and with the hyperintensities in the bilateral temporopolar white matter. The ToM total score was also associated with hyperintensities in the bilateral temporo-parietal and left frontal white matter. Multivariate models based on these parameters allowed a better prediction of the ToM total score ($R^2 = 0.49$) and cognitive subscore ($R^2 = 0.52$) than univariate models. There was no association between ToM measures and cortical thickness, nor between brain MRI measures and affective subscore/error types.

Conclusions: The ToM cognitive involvement in DM1 is associated with both the gyrification in the right superior parietal gyrus and the volume of hyperintensities in the anterior-temporal white matter, suggesting the possible joint implication of a neurodevelopmental phenomenon and disconnections arising from white matter changes.

1 | Introduction

Theory of mind (ToM) refers to the ability to infer others' mental states to predict their behavior, which is crucial for successful social interactions [1]. ToM can be divided into cognitive ToM (ability to infer what others think/believe) and affective ToM (ability to infer what others feel/experience) which can be differently impaired [1]. Moreover, ToM impairment may manifest as

an inability to detect and interpret social cues in an interpersonal situation (absence of mentalization), a reduction of this ability (hypomentalization), or conversely the over-interpretation of these cues (hypermentalization) [2]. This separation of ToM into different processes is reinforced by the differential impairment observed in several neurologic/psychiatric disorders. Indeed, the affective and cognitive components of ToM can be selectively disturbed in Alzheimer's disease or fronto-temporal dementia [3], and are associated with different demographic parameters, cognitive domains, and brain areas [4] in Parkinson's disease. Hypermentalizations were associated with positive symptoms in schizophrenia, whereas hypomentalizations were correlated with disorganized symptoms [5].

Brain MRI studies showed that ToM tasks engage a particular network ("ToM network") involving the medial pre-frontal and posterior cingulate cortex, the temporo-parietal junction, the precuneus, the posterior superior temporal sulci, the bilateral temporopolar lobes, and the amygdala [6]. Brain areas activated during affective/cognitive ToM tasks [7] or during hypomentalization/hypermentalization errors [8] differ, which may explain the selective involvement observed in some neurological diseases altering selectively some brain regions. Studying diseases with a specific ToM impairment profile (e.g., affective more impaired than cognitive ToM) such as in myotonic dystrophy type 1 (DM1) may allow a better delineation of brain areas implicated in the different ToM processes [9].

DM1 is a multisystem genetic disease caused by CTG triplet repeat expansion in the *DMPK* gene. DM1 patients also frequently present muscular, cardiac, respiratory, endocrine, gonadal, and/or brain involvement. This brain involvement results in cognitive and behavioral problems which vary from one patient to another [10], but frequently affect social abilities [11–15]. Many studies highlighted social cognition impairments in DM1 [11], more specifically ToM deficits [9, 11–15]. We previously observed a specific profile of ToM impairment in DM1, with predominant hypomentalizations concerning the affective component [9].

DM1 is associated with brain MRI abnormalities [16], whose localization seems to overlap with the brain areas implicated in affective ToM. For instance, DM1 patients often display temporopolar white matter hyperintensities (WMH) [16], the temporal pole being part of the ToM affective network. Gyrification, occurring during neurodevelopment, has been shown to be abnormal in DM1 in frontal and parieto-occipital areas [17], which might also be implicated in ToM. Cortical atrophy, a marker of neurodegeneration [16], is also observed in DM1, predominating in the precuneus, the superior temporal gyrus, the medial frontal gyrus, and the anterior cingulate cortex [14] all involved in the ToM affective network. MRI measures have been associated with ToM impairment in DM1, such as the white matter, supratentorial volumes [9], and right inferior temporal gyrus volume [15], or an increased functional connectivity between the left inferior temporal and fronto-cerebellar nodes [12]. Nevertheless, MRI correlates of affective versus cognitive ToM involvement, and of error types, have never been studied in DM1.

We made the hypothesis that the specific profile of ToM impairment in DM1 can be related to specific topographies of brain abnormalities of degenerative or neurodevelopmental origin.

2 | Material and Methods

2.1 | Participants

We included patients from the DMVASCOG cohort (NCT04656210) [9]. Briefly, this cohort is composed of symptomatic adults with genetically proven DM1 who underwent, in a 12 months interval, neuropsychological evaluations and brain MRI in the absence of contraindications (e.g., pacemaker, claustrophobia). Social cognition was only evaluated in patients with an estimated intellectual quotient (IQ) superior to 70, as social cognition is a high-order function. The IQ was estimated through the administration of four tasks (vocabulary, similitudes, cubes, and matrices) from the Weschler Adult Intelligence Scale—Third Edition (WAIS-III) [18] as proposed by Grégoire and Wierzbicki [19]. Here, we only included patients who had both an evaluation of social cognition and a brain MRI. These investigations were approved by the Ethical Committee of Bordeaux, France (no. 2020-082B).

2.2 | Measures

2.2.1 | Movie for the Assessment of Social Cognition

The MASC evaluation was fully described in [9]. Briefly, it is a 15-min movie showing social interactions between four people having dinner, thus depicting real-life social interactions. At different timepoints during the movie, a multiple-choice question is asked to the participant about a character's emotions or thoughts. For each patient, we obtained a total MASC score, subscores for affective/cognitive ToM, and the proportion of the different error types (absence of mentalization, hypomentalization, and hypermentalization).

2.2.2 | Clinical and Laboratory Measurements

We collected the age at symptom onset, duration of DM1 (time interval between symptoms onset and neuropsychological examination), muscle impairment rating scale (MIRS), and the CTG triplets expansion size in leukocytes at the diagnosis.

2.2.3 | Magnetic Resonance Imaging

MRI images were acquired on a 3-Tesla brain MRI (Achieva, Philips, Best, Netherlands), using a 32-channel array head coil. The protocol included a 3D-T1 gradient-echo (TR/TE = 7.2/3.3 ms, flip angle = 9°, FOV = $256 \times 240 \times 176\,mm^3$, voxel size = $1 \times 1 \times 1\,mm^3$) and a 3D-Fluid-Attenuated Inversion Recovery (FLAIR) sequence (TR/TE = 8000/333.6 ms, flip angle = 40°, FOV = $250 \times 250 \times 180\,mm^3$, voxel size = $1.12 \times 1.12 \times 1.12\,mm^3$).

Complete description of MRI processing is available as Supporting Information. Shortly, the software FreeSurfer was used to segment different brain structures from the 3D-T1 sequence and to compute cortical thickness and local gyrification index (LGI) maps. The software ITK-SNAP was used for the semi-automatic measurement of the volume of WMH on 3D-FLAIR images, normalized on the intracranial volume (FreeSurfer).

2.3 | Statistics

We used a one-tailed Crawford's test (single case) to compute the proportion of DM1 patients impaired regarding the MASC total score and affective/cognitive subscores [20].

We studied associations of ToM measures with cortical thickness/LGI maps using FreeSurfer, and with WMH using Multivariate Lesion-Symptom Mapping with Support Vector Regression [21] (more details in Supporting Information). We used the Tractotron software to determine in which white matter tract the WMH of interest was located. To analyze together the results from these different analyses, we included them in multivariate linear models, using a level of significance of 0.05 with a Bonferroni correction.

3 | Results

At the time of analysis, the DMVASCOG cohort included 124 DM1 patients [22]. Only 92 had an estimated IQ > 70 and underwent the MASC. MRI was not performed in 26 because of pacemaker (14 patients), not attending the appointment (8 patients), claustrophobia (2 patients), refusal (1 patient) or morbid obesity (1 patient). Eight patients were excluded because of an incomplete MRI protocol (2 patients) or because of a delay over 1 year between the MRI and neuropsychological examination (6 patients), leading to 58 included patients (Table 1). The included patients only differed from the excluded ones regarding education and the MIRS score (Table 1). Based on the age at symptoms onset [23], 1 DM1 patient (1.7%) had a childhood-onset form, 16 (27.6%) had a juvenile form, 25 (43.1%) an adult form, and 16 (27.6%) a late-onset form. Compared to a control population [9], 24/58 (41.4%) had an impaired total MASC score; 26/58 (44.8%) had an impairment of the affective subscore, whereas 16/58 (27.6%) had an impairment of the cognitive subscore (Table 2). Only 3/58 (5.2%) had a selective impairment of the cognitive subscore with a normal affective subscore. Comparisons between included patients and controls are shown in Table S1.

3.1 | Cortical Thickness

We studied cortical thickness, adjusting for age and IQ. No significant association of ToM measures (MASC total score, emotional and cognitive subscores, number of absence of

TABLE 1 | Demographics and cognitive data from our 58 DM1 patients.

Measures	Included patients ($n = 58$)	Excluded patients ($n = 66$)	p
Demographics			
Gender	29 F (50%) 29 M (50%)	37 F (56.1%) 29 M (43.9%)	0.67
Age (years)	43.1 ± 13.3	46.9 ± 13.6	0.12
Age of DM1 onset (years)	30 ± 15.4	30.8 ± 16.0	0.79
DM1 duration (years)	13.1 ± 9.5	16.1 ± 10.6	0.10
Educational level (years)	12.3 ± 3.1	10.4 ± 2.8	**< 0.001**
CTG triplets' expansion size ($n = 57$)	449.3 ± 290.8	525.2 ± 396.5	0.30
MIRS	1: 6 (10.3%) 2: 20 (34.5%) 3: 22 (37.9%) 4: 10 (17.2%)	1: 4 (6.1%) 2: 19 (28.8) 3: 27 (40.9%) 4: 16 (24.2%)	**< 0.001**
Cognition			
MASC total score (%)	60.7 ± 12.6	—	—
Affective subscore (%)	57.6 ± 13.9	—	—
Cognitive subscore (%)	62.4 ± 16.7	—	—
Absence of mentalizations errors (%)	7.2 ± 6.0	—	—
Hypomentalizations errors (%)	18.6 ± 8.3	—	—
Hypermentalizations errors (%)	13.5 ± 5.8	—	—
Intellectual quotient	86.4 ± 13.0	75.5 ± 16.0	**< 0.001**
Brain MRI Measures			
Mean cortical thickness (mm)	2.39 ± 0.08	—	
Intracranial volume (cm^3)	1305.2 ± 238.3	—	
White matter hyperintensities volume (cm^3)	5.4 ± 6.1	—	

Note: Quantitative data are expressed as mean ± standard deviation and compared between included and excluded patients using a t-test, and qualitative as number (percentage) and compared between included and excluded patients using a χ^2 test. Significant p-values are displayed in bold.

mentalization, hypomentalization and hypermentalization errors) was observed with either the mean cortical thickness or cortical thickness maps.

3.2 | Intracranial Volume and LGI

We studied associations between ToM and neurodevelopmental features. No association between ToM and the total intracranial volume was found (Table 3). Looking at associations between the LGI and ToM adjusting for IQ, we observed a significant positive association between the MASC total score and the LGI in the right superior parietal gyrus (Figure 1, MNI coordinates of the peak of the significant cluster [23, −61, 40]). The cognitive subscore was also positively associated with the LGI of the right superior parietal gyrus (Figure 1, MNI coordinates of the peak of the significant cluster [24, −63, 38]). There was no significant association of the LGI with other ToM measures (affective subscore, absence of mentalization, hypomentalization and hypermentalization errors).

TABLE 2 | Distribution of ToM subscore impairments in our population.

		Affective		
		Impaired	Not impaired	Total
Cognitive	Impaired	13	3	16
	Not impaired	13	29	42
	Total	26	32	58

3.3 | White Matter Hyperintensities

We studied the associations between ToM and WMH. The probability map of WMH is displayed in Figure S1. There was no significant association between ToM and the WMH volume (Table 3). To look for associations with locations of WMH, we used Lesion-Symptom Mapping. We failed to predict the affective subscore and the different types of errors, but succeeded for the total MASC score and cognitive subscore. The total MASC score was associated with hyperintensities in the bilateral temporopolar white matter, bilateral temporo-parietal white matter, and left frontal white matter ($C=50$; gamma = 0.1; accuracy = 0.15; reproducibility = 0.78; Figure 2). The cognitive subscore was associated with hyperintensities in the bilateral temporopolar white matter ($C=40$; gamma = 2; accuracy = 0.28; reproducibility = 0.86; Figure 2).

Using the Tractotron software, we were able to determine which white matter tracts may potentially be interrupted by these WMH. The temporopolar WMH associated with the cognitive subscore were located in the bilateral uncinate fasciculus and bilateral inferior longitudinal fasciculus (Table 4). The

TABLE 3 | Association of ToM with the mean cortical thickness, the estimated total intracranial volume, and the white matter hyperintensities volume adjusting on age and intellectual quotient (multivariate linear models; β is the regression coefficient and p its corresponding p-value).

	Mean cortical thickness		Intracranial volume		White matter hyperintensities volume	
ToM measure	β	p	β	p	β	p
MASC total score	10.3	0.25	1.9	0.50	−0.17	0.14
Affective subscore	31.6	0.21	−3.3	0.68	−0.48	0.14
Cognitive subscore	19.4	0.47	9.0	0.28	−0.38	0.27
Absence of mentalization	−3.4	0.49	−0.8	0.60	0.07	0.26
Hypomentalizations	−10.2	0.10	−1.9	0.35	0.05	0.66
Hypermentalizations	3.4	0.48	0.8	0.61	0.06	0.29

FIGURE 1 | Significant associations between the local gyrification index in the right superior parietal cortex and the MASC total score (left), and the cognitive subscore (right).

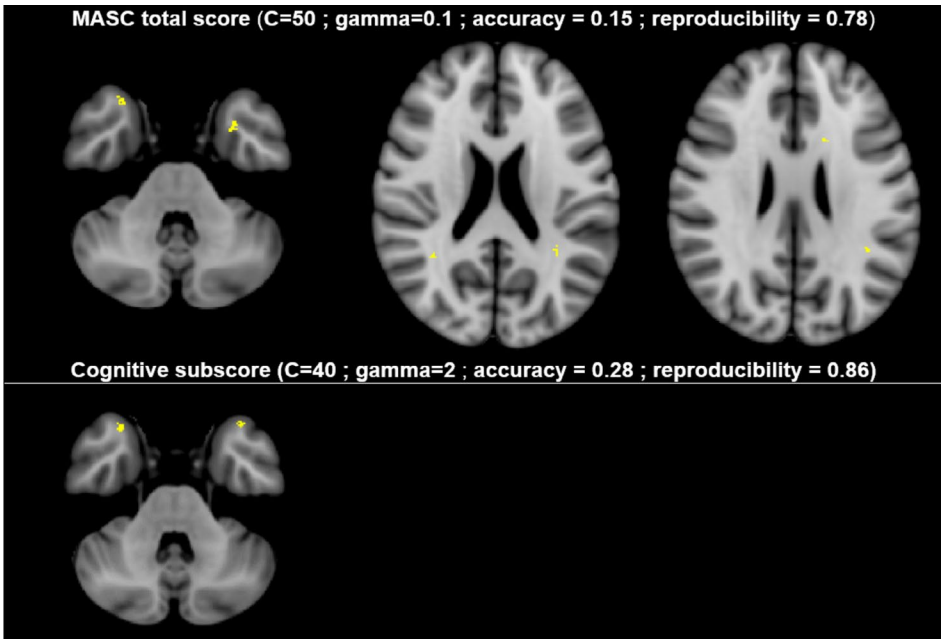

FIGURE 2 | Significant associations (yellow) between white matter hyperintensities and theory of mind scores.

TABLE 4 | Probabilities for the white matter hyperintensities to be located in a given white matter tract.

White matter tract	Side	Probability
White matter hyperintensities associated with the MASC score		
Uncinate fasciculus	Right	0.98
Inferior longitudinal fasciculus	Left	0.89
	Right	0.93
Inferior fronto-occipital fasciculus	Left	0.86
	Right	0.72
Long segment of the arcuate fasciculus	Left	0.98
	Right	0.84
Posterior segment of the arcuate fasciculus	Left	0.78
	Right	0.96
Superior longitudinal fasciculus (II: major component)	Left	094
	Right	0.93
Superior longitudinal fasciculus (III: ventral component)	Left	0.86
Corpus callosum	—	1
Frontal commissure	—	1
White matter hyperintensities associated with the cognitive subscore		
Uncinate fasciculus	Left	0.92
	Right	0.96
Inferior longitudinal fasciculus	Left	0.76
	Right	0.78

Note: Only probabilities > 0.7 are considered.

temporopolar WMH associated with the MASC score were located in the right uncinate fasciculus and bilateral inferior longitudinal fasciculus. The more posterior WMH associated with the MASC score were located in the bilateral inferior fronto-occipital fasciculus, bilateral arcuate fasciculus (long and posterior segments), bilateral major component and left ventral component of the superior longitudinal fasciculus, corpus callosum, and frontal commissure.

Considering the significant associations with gyrification measures as well as WMH, we ran complementary analyses to evaluate their potential additive contribution to the ToM scores. We extracted for each patient the mean LGI in the right superior parietal gyrus and the volume of WMH in the areas identified by the lesion-symptom mapping analysis and included them in univariate and multivariate linear models. The total MASC score remained significantly associated with the WMH in the temporopolar and frontal white matter and with the gyrification index in the superior temporal gyrus in univariate models (Table 5). Among all these univariate models, the highest R^2 was 0.27 for the model including the WMH in the temporopolar white matter. In the multivariate model, previous associations remained significant except for the WMH in the frontal white matter; the R^2 of the total model increased to 0.49. The cognitive subscore remained significantly associated with both the WMH volume in the temporopolar white matter and the gyrification index in the superior parietal gyrus in univariate models (Table 6). Among all these univariate models, the highest R^2 was 0.35 for the model including the WMH in the temporopolar white matter. In the multivariate model, previous associations remained significant; the R^2 of the total model increased to 0.52. Those results were not modified by adjusting neither on the CTG triplets' number (Tables S2 and S3) nor on the age at DM1 onset (Tables S4 and S5).

4 | Discussion

In our population, we found that the MASC total score and cognitive subscore were both associated with the LGI in the same area of the right superior parietal gyrus. Concerning WMH, the MASC total score was associated with the bilateral temporopolar WMH, and in the bilateral temporo-parietal and left frontal white matter, located in the inferior fronto-occipital fasciculus, arcuate fasciculus, superior longitudinal fasciculus, and corpus callosum and frontal commissure. The cognitive subscore was also associated with the bilateral temporopolar WMH, located inside the uncinate and inferior longitudinal fasciculi. We found no association between the brain MRI measures and neither the affective subscore nor error types (absence of mentalization, hypomentalizations, hypermentalizations). There was also no association of the ToM measures with brain overall measures (mean cortical thickness, estimated total intracranial volume, WMH volume), neither with cortical thickness maps.

The location of these brain MRI abnormalities associated with ToM is consistent with previous studies in other diseases or healthy controls. A study on surgery of brain tumors found an impairment of cognitive but not affective ToM in patients with right superior parietal damage [24], which is the cortical area in which the LGI was associated with cognitive but not affective ToM. We found an association of the MASC total score and

TABLE 5 | Association of the total MASC score with the white matter hyperintensities volume in the areas identified by the lesion symptom mapping analysis in the temporopolar white matter ($WMH_{LSMtemporal}$), in the frontal white matter ($WMH_{LSMfrontal}$), in front of the temporo-parietal junction ($WMH_{LSMposterior}$), and with the local gyrification index in the superior parietal gyrus (LGI) in univariate linear models and a multivariate model (MASC total score – $WMH_{LSMtemporal}$ + $WMH_{LSMfrontal}$ + $WMH_{LSMposterior}$ + LGI).

	Univariate models			Multivariate model		
MASC total score	**β**	***p***	**Adj. R^2**	**β**	***p***	**Adj. R^2**
$WMH_{LSMtemporal}$	−167.1	**<0.001**	0.27	−140.6	**<0.001**	0.49
$WMH_{LSMfrontal}$	−0.8	**<0.001**	0.21	−0.5	0.035	
$WMH_{LSMposterior}$	−0.12	0.008	0.1	0.01	0.868	
LGI	15.1	**<0.001**	0.21	11.2	**0.001**	

Note: β is the regression coefficient, *p* its corresponding *p*-value, and Adj. R^2 the adjusted *R*-squared of the model. Using a Bonferroni correction, level of significance was set at 0.05/8 = 0.00625. Significant *p*-values are displayed in bold.

TABLE 6 | Association of the cognitive subscore with the white matter hyperintensities volume in the anterior part of the temporal lobe ($WMH_{LSMtemporal}$), and with the local gyrification index in the superior parietal gyrus (LGI) in univariate linear models and a multivariate model (Cognitive subscore – $WMH_{LSMtemporal}$ + LGI).

	Univariate model			Multivariate models		
Cognitive subscore	**β**	***p***	**Adj. R^2**	**β**	***p***	**Adj. R^2**
$WMH_{LSMtemporal}$	−1235.5	**<0.001**	0.35	−1113.1	**<0.001**	0.52
LGI	47.2	**<0.001**	0.24	40.0	**<0.001**	

Note: β is the regression coefficient, *p* its corresponding *p*-value, and Adj. R^2 the adjusted R-squared of the model. Using a Bonferroni correction, level of significance was set at 0.05/4 = 0.0125. Significant *p*-values are displayed in bold.

cognitive subscore with the volume of temporopolar WMH, in the surrounding area of the temporopolar cortex which has been associated with both cognitive and affective ToM [7]. The MASC total score was also associated with the volume of temporo-parietal WMH, next to the temporo-parietal junction which plays a major role in assigning mental states to others and thus to ToM [7]. These WMH are located in white matter tracts which were previously linked with ToM such as the uncinate [25], the inferior longitudinal, the inferior fronto-occipital, the arcuate and the superior longitudinal fasciculus [26]. This concordance suggests that the ToM network in DM1 patients has similar components to non-DM1 individuals, as found in a study which showed no topological differences in the ToM network observed with functional MRI between DM1 patients and healthy controls [12].

This ToM network might be impaired by different mechanisms. Gyrification is a process occurring during neurodevelopment. The positive association between the LGI in the right superior parietal gyrus and cognitive ToM might suggest a neurodevelopmental mechanism, with a lower gyrification in this area resulting in worse cognitive mentalization performance. Early-onset DM1 can be viewed as a neurodevelopmental disorder [17], a population in which gyrification has been shown to be abnormal in frontal and parieto-occipital cortices. Therefore, we hypothesize that some DM1 patients may have a lower gyrification in the right superior parietal gyrus, evoking an abnormal development of this area implicated in the cognitive ToM network [24], therefore impacting selectively cognitive ToM and accordingly the overall ToM. This hypothesis may explain the association previously found between the overall ToM and CTG triplet repeat expansion size [9], as a higher number of triplets is associated with an increased risk of neurodevelopmental involvement in DM1 [17]. Further analyses are needed to confirm this hypothesis.

We also found an association between ToM and the volume of WMH in various areas, including the temporopolar white matter, which is a typical location of hyperintensities in DM1 [16]. An association between social cognition and WMH in the frontal, temporal, and insular subcortices has previously been observed in DM1 [27], and the white matter involvement has been suggested to be the predominant brain change in DM1 [28]. A disconnection mechanism due to this white matter involvement has consequently been suggested to explain cognitive changes in DM1 [29], as in other conditions such as stroke [30]. We hypothesize that the WMH in DM1 may occur in some strategic locations that disconnect cortical areas involved in the ToM network, leading to ToM impairments. The temporopolar white matter may be one of these strategic locations, and the high frequency of WMH in this brain area in DM1 may explain the high prevalence of ToM disturbances [10]. A previous study found an association between ToM abilities in DM1 and an increased connectivity of different cortical areas with the inferior temporal gyrus [12]. This hyperconnectivity might be a rearrangement to compensate for disconnections in other parts of the ToM network.

The nature of the WMH in DM1 is not yet fully determined. They are observed in congenital DM1 [31], even during the neonatal period and childhood [32], suggesting WMH can be at least partly neurodevelopmental. Nevertheless, temporopolar WMH are not observed in congenital and childhood DM1 [31], and WMH are increasing with time in adult DM1 [31, 33], showing their potentially progressive nature. Several results suggest a vascular origin. In addition to loss of myelin with a varying amount of axonal loss, brain pathology in DM1 shows dilated perivascular spaces, gliosis, and capillary hyalinization in deep and subcortical white matter [34]. The dilated perivascular spaces can also be highlighted using brain MRI and are co-localized with WMH in the temporopolar white matter [35]. Nevertheless, cerebral small vessel disease seems unlikely to fully explain WMH in DM1, as classical hallmarks such as microbleeds and lacunes are not observed [34] and temporopolar WMH are not observed in typical cerebral small vessel disease. Thus, other mechanisms of vascular involvement may occur in DM1. For instance, the TAU protein accumulation leading to neurofibrillary tangles observed in DM1 may have a role in the formation of dilated perivascular spaces because of astrocytic dysfunction, as perivascular spaces have been associated with the burden of neurofibrillary tangles in other tauopathies such as Alzheimer's disease [36]. Microvascular changes leading to a lack of drainage of interstitial fluid and accumulation of degraded proteins have also been suggested to explain the temporopolar WMH in DM1 [35]. This mechanism may also occur in the genetic cerebral small vessel disease named cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [37], in which temporopolar WMH are also common. If our hypothesis on the role of temporopolar WMH in ToM involvement is correct, a ToM impairment should also be common in CADASIL. Yet, only a few data suggest a ToM involvement in CADASIL [38, 39], without any study of the associations with brain MRI.

Our results found evidence for both neurodevelopmental and neurodegenerative possible mechanisms to explain the ToM impairment in DM1. One might expect that one of these mechanisms is more predictive of ToM performance than the other. Our analysis did not agree with this hypothesis, as the combination of both factors in multivariate models gave a better prediction of the total MASC score and cognitive subscore (approximately 50% of the variance) than univariate models (between approximately one-fifth to one-third of the variance). This suggests that the gyrification in the parietal superior gyrus and of the WMH are two different phenomena, acting each one separately mainly on the cognitive aspect of ToM, which is consistent with their different localization (cortex versus white matter) and their different possible origins (developmental versus acquired). Altogether, our results may suggest the following model for ToM involvement in DM1. A cognitive ToM network exists in DM1, implicating as in non-DM1 individuals the temporal pole and the right superior temporal gyrus. This network can be separately impacted by two different mechanisms: a developmental involvement leading to a lower gyrification in the right superior temporal gyrus, and potentially acquired temporopolar WMH which can disconnect the ToM network, both leading to cognitive ToM involvement.

We found no association between the brain MRI measures and the affective subscore, which was more frequently impaired than the cognitive component, as in our previous work [9]. Several hypotheses can be made. The affective ToM network might be

more distributed, and therefore more localizations of brain lesions may be implicated than for cognitive ToM; the neural basis of this affective ToM impairment might thus be more difficult to highlight. The affective ToM performance might also depend on a higher number of factors and be more multidetermined than the cognitive ToM subscore; therefore, association with focal regions of the brain might be more difficult to find. Finally, the neural mechanisms of affective ToM involvement in DM1 may rely on parameters not studied by our brain MRI measures, such as the amygdala volume which has been associated with the affective subscore of the MASC [40].

We neither observed an association between brain MRI measures and ToM error types (absence of mentalization, hypomentalizations, hypermentalizations), which may be explained by a lack of power compared to other brain measures, as all error types contribute to the ToM performance.

Finally, we found no association of ToM with cortical thickness. Other authors found an association of ToM only with the atrophy of small regions of the right parahippocampal and inferior temporal gyrus in DM1 [15]. Conversely, in populations other than DM1 patients, several studies found associations between the thickness of some cortical areas and MASC scores [41–43]. As cortical thickness has been related to a neurodegeneration in DM1 [44] and the ToM network involves many cortical areas [7], our results suggest that ToM is not strongly influenced by a potential cortical neurodegenerative mechanism, contrary to the hypothesis made for other cognitive functions [44].

Our study has some limits. The number of patients included in the study was not extensive, as DM1 is a rare disease. As theory of mind is a higher-order cognitive function, we only studied it in patients with an estimated IQ over 70; therefore, our population is not fully representative of all DM1 patients (more educated). Our included patients also have a stronger motor involvement than the initial cohort, maybe because of a milder DM1 severity. Moreover, many DM1 patients have a cardiac pacemaker, which is an MRI contraindication. We studied only adult patients; our findings might have been different in DM1 children or teenagers. Finally, the relationships highlighted are not necessarily causal but are used to generate hypotheses that might help to guide future studies.

To conclude, the ToM involvement in DM1 seems associated with both the gyrification in the right superior parietal gyrus and volume of temporopolar WMH, which might suggest the joint implication of a neurodevelopmental phenomenon and disconnections from white matter disruptions. These associations were found specifically for cognitive ToM. Our findings must be confirmed by further studies on other populations and longitudinal data, using different imaging modalities such as functional MRI, and studying deeper the mechanism of disconnection in DM1.

Author Contributions

Jean-Baptiste Davion: investigation, writing – original draft, writing – review and editing. **Céline Tard:** conceptualization, investigation, funding acquisition, writing – review and editing. **Romain Viard:** investigation, writing – review and editing. **Loren Fragoso:** writing – review and editing, investigation. **Amina Wilu-Wilu:** investigation, writing – review and editing. **Luc Defebvre:** writing – review and editing. **Grégory Kuchcinski:** investigation, writing – review and editing. **Xavier Delbeuck:** conceptualization, investigation, funding acquisition, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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