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Characterization of theory of mind performance in patients with myotonic dystrophy type 1

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ABSTRACT

Introduction: Myotonic dystrophy type 1 (DM1) is associated with motor dysfunction as well as psychological and cognitive impairments, including altered social cognition. Theory of mind (ToM) impairments have been reported in this disease but their nature and their cognitive/cerebral correlates have yet to be determined.

Methods: Fifty DM1 patients and 50 healthy controls were assessed using the Movie for the Assessment of Social Cognition, which quantifies impairments in affective and cognitive components of ToM through the depiction of everyday situations. We also measured the study participants' cognitive, behavioral and social abilities, quality of life, and brain MRI characteristics.

Results: DM1 patients presented a significant impairment in ToM performance compared to controls ($p < .001$). The patients' errors were related to hypomentalizations ($p < .001$ *vs* controls) but not to hypermentalizations ($p = .95$). The affective component was affected ($p < .001$ *vs* controls) but not the cognitive component ($p = .09$). The ToM impairment was associated with demographic variables (older age and a lower educational level), genetic findings (a larger CTG triplets repeat expansion) and cognitive scores (slower information processing speed). Associations were also found with brain MRI variables (lower white matter and supratentorial volumes) but not with behavioral or social variables.

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Discussion: DM1 patients display a ToM impairment, characterized by predominant hypomentalizations concerning the affective component. This impairment might result from structural brain abnormalities observed in DM1.

Abbreviations

ANOVA	analysis of variance
BECS-GRECO	Groupe de réflexion sur les évaluations cognitives – neuropsychological semantic battery
CSCT	computerized speed cognitive test
DM1	myotonic dystrophy type 1
HADS	hospital anxiety and depression scale
HVLT	Hopkins Verbal Learning Test
IQ	intellectual quotient
LARS	Lille Apathy Rating Scale
MASC	Movie for the Assessment of Social Cognition
MIRS	Muscular Impairment Rating Scale
QFS	Questionnaire de Fonctionnement Social
TMT	Trail Making Test
ToM	theory of mind
VOSP	Visual Object and Space Perception
WAIS	Weschler Adult Intelligence Scale
WHOQOL-BREF	World Health Organization Quality of Life Brief Version

1. Introduction

Myotonic dystrophy type 1 (DM1 or Steinert's disease) is a multisystem genetic disease caused by CTG triplets repeat expansion in the *DMPK* gene. DM1 is the most frequent adult-onset myopathy; its prevalence ranges from .5 to 18.1 per 100,000 (Theadom et al., 2014). The muscle-related symptoms typically include myotonia (delayed relaxation of skeletal muscles), amyotrophy and muscle weakness, predominantly in distal and facial muscles. In addition to muscle impairment, DM1 patients also frequently present cardiac, respiratory, endocrine and/or gonadal disorders, cognitive impairments and behavioral problems. Behavioral problems vary considerably from one patient to another, including for example autistic traits, apathy, depression, anxiety, fatigue and excessive daytime sleepiness (Okkersen, Buskes, et al., 2017; van der Velden et al., 2019). The cognitive impairments also vary markedly from one patient to another (Okkersen, Buskes, et al., 2017) but frequently affect social abilities (Kobayakawa et al., 2010, 2012; Labayru et al., 2018; Serra et al., 2016, 2020; Takeda et al., 2009; Winblad et al., 2006), and interestingly, many studies highlighted difficulties in interpersonal relationships and thus social interactions in DM1 (Minier et al., 2018).

Some researchers have hypothesized that these disturbances are related to impairments in social cognition (Kobayakawa et al., 2012), several studies showing social cognition deficits in DM1 using a variety of tasks, such as the "Reading the Mind in the Eyes" test (Kobayakawa et al., 2012; Serra et al., 2016), faux pas recognition test (Kobayakawa et al., 2012), facial emotion recognition test (Labayru et al., 2018), emotion attribution test, and social situations test (Serra et al., 2020). Interpersonal difficulties could be notably related to deficits in theory of mind (ToM) (Kobayakawa et al., 2012; Labayru et al., 2018; Serra et al., 2016, 2020), which refers to the ability to infer other people's mental states to predict their behavior or actions (Premack & Woodruff, 1978). However, studies showing ToM impairments in DM1 patients only used non-ecological tests which may not reflect daily-life situations. Furthermore, these studies did not explore the nature of this ToM impairment. Indeed, ToM can be divided into a cognitive component (i.e. the ability to infer what other individuals think or believe) and an affective component (i.e. the ability to infer what other individuals feel or experience) which can be differentially involved (Shamay-Tsoory & Aharon-Peretz, 2007). Moreover, ToM reasoning can be impaired through an inability to detect and interpret social cues in an interpersonal situation (absence of mentalization), a reduction of this ability (hypomentalization), or in contrast, the over-interpretation of these cues (hypermentalization) (Dziobek et al., 2006).

Process dissociation of ToM abilities have been document in different neurological [such as behavioral variant frontotemporal dementia (Le Bouc et al., 2012) or Pakinson's disease (Maggi et al., 2022)], psychiatric [such as schizophrenia (Fretland et al., 2015)] and neurodevelopmental [such as autism spectrum disorders (Kimhi, 2014)] conditions. For example, behavioral variant frontotemporal dementia is a neurodegenerative disease that is characterized by behavioral disturbances which compromised interpersonal relationships. In the early phase of this disease, affective ToM disorders have been observed while cognitive ToM disorders seem to appear later in the disease (Torralva et al., 2015). In psychiatric diseases, symptoms of some pathologies have also been linked to different processes dysfunctions of ToM, e.g. hypermentalizations have been associated with the positive symptomatology observed in schizophrenia, whereas hypomentalizations were associated with disorganized symptoms (Fretland et al., 2015).

Hence, we used in our study the Movie for the Assessment of Social Cognition (Dziobek et al., 2006) (MASC) which allows the discrimination between the two components of ToM (affective/cognitive) but also the error type (absence of mentalization/hypomentalization/hypermentalization) to characterize the ToM impairment in DM1 patients. Given that the literature data have revealed emotional problems and impairments in ToM abilities, we hypothesized that DM1 patients might be more impaired in affective ToM than in cognitive ToM, and examined the error profile. We also

explored if this ToM impairment was associated with clinical variables (disease characteristics, cognitive performance, behavioral scores, and quality of life), genetic factors (e.g., CTG triplets repeat expansion), and imaging features (brain atrophy and white matter hyperintensities, which are the most frequent structural MRI abnormalities in DM1 (Okkersen, Monckton, et al., 2017)).

2. Material and methods

Our data are part of the larger DMVASCOG study (NCT04656210) for which other analyses are ongoing. No part of the study procedures and analyses was pre-registered prior to the research being conducted. No analysis code was used. Here we report all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established priori to data analysis, all manipulations, and all measures in the study. No sample size calculation was performed.

2.1. *Participants*

We included 50 DM1 patients from the DMVASCOG cohort (NCT04656210) in the study. This cohort is composed of symptomatic adults (age ≥18) with genetically proven DM1 (i.e., >50 CTG triplets repeats in the *DMPK* gene, measured in leukocytes) consulting in the Neuromuscular Unit at Lille University Hospital (Lille, France). The main exclusion criteria were a history of other neurological conditions than DM1, any major condition or disorder that was likely to interfere with the study evaluations (including cancer and uncontrolled cardiopathy), pregnancy, inability to express informed consent. As social cognition is a high-order function, it was evaluated only in patients without significant intellectual disability [i.e., an estimated intellectual quotient (IQ) below 70]. In addition to the ToM evaluation, each participating patient with DM1 underwent clinical and neuropsychological evaluations and brain MRI. These investigations were approved by Ethical Committee of Bordeaux, France (*Comité de Protection des Personnes Sud-Est III*, Bordeaux, n°2020-082B). We included the 50 first patients of the DMVASCOG cohort who had an evaluation of social cognition.

Fifty healthy volunteers constituted a control group: 34 were recruited through the Catholic University of Louvain (Louvain, Belgium) (Maurage et al., 2016), and 16 were recruited through the University of Lille (Lille, France). Exclusion criteria were a history of neurological, psychiatric or major medical conditions, or any condition which may interfere with the cognitive and behavioral evaluation. Demographic characteristics (sex, educational level and age at the time of the neuropsychological evaluation) were recorded for DM1 patients and controls.

2.2. *Measures*

2.2.1. *Movie for the Assessment of Social Cognition*

The MASC has been used to study ToM in healthy subjects (Allain et al., 2019; Laillier et al., 2019) but also in different neurological (e.g., multiple sclerosis (Kraemer et al., 2013), epilepsy (Metternich et al., 2022)) and psychiatric (e.g., schizophrenia (Fretland et al., 2015), depression (Wolkenstein et al., 2011), social anxiety (Lenton-Brym et al., 2018)) diseases. It is a 15-min high-resolution movie that shows social interactions between four people having dinner together and thus depicting real-life social interactions. The protagonists interact and express positive or negative emotions, intentions and thoughts. The study participants are instructed to watch the movie attentively and infer the characters' thoughts or feelings; the movie is paused regularly so that the study participant could be questioned. After watching each of the 45 video sequences (lasting from 3 to 71 sec), the participant has to answer a multiple-choice question about a character's emotions, feelings, intentions, or thoughts; the latter could be inferred from verbal cues (semantic content of characters' speech), nonverbal cues (facial expressions, prosody, body language), and contextual cues. For each question, four possible written answers are provided, with one from each of the following categories: the correct answer (i.e., the correct identification of a character's mental state), an absence of mentalization (i.e., total inability to infer a character's mental state), hypomentalization (poor or insufficient ToM inference), and hypermentalization (i.e., overinterpretation of a character's mental state). For example, during a scene of the MASC: Sandra, Betty, Michael, and Cliff are preparing the meal. Betty asks Sandra how many cups of cream are needed for the sauce. Anna answers that she should add 2 cups of creams, and then Michael says to Betty: "If it was up to you, you would have put 5 cups of cream, wouldn't you ?". The video then shows the face of Betty who seems offended by Michael's remark. The video stops, and the participant is asked about Betty's feeling with a multiple-choice question. One choice reflect a correct interpretation of Betty's feeling, the 3 others different types of error: (1) She is offended by the remark of Michael (correct answer); (2) She hates Michael and would prefer that he leaves the place (hypermentalization); (3) Five cups of cream is definitively too much for the sauce (absence of mentalization); (4) Betty is surprised that Michael knows she likes cream (hypomentalization).

The total MASC score was expressed as the proportion of correct answers, in percentage. We also computed the affective versus cognitive subscores (Buhlmann et al., 2015; Maurage et al., 2016), and perceptive versus contextual subscores (Wilbertz et al., 2010), based on information provided by the original author of the MASC through personal communication. The affective ToM subscore is the percentage of correct answers when considering only the 15 questions specifically related to the characters' feelings or emotions (e.g., disappointment or surprise), whereas the cognitive ToM was focused on the 18 questions specifically related to the characters' intentions or thoughts (e.g., action plans, aims and beliefs). The perceptive subscore is the percentage of correct answers when considering the 11 questions specifically requiring recognition of characters reaction (through perceptive cues, such as voice, facial expression and body posture), whereas the contextual subscore was derived from the 18 questions requiring an interpretation of the situation and character's background and motives. The proportions of errors related to absence of mentalization, hypomentalization and hypermentalization were calculated for the MASC total score and for each MASC subscales. The MASC displays high

levels of internal consistency (Cronbach's alpha >.82 for the total scale and for each subscale), interrater reliability and test-retest reliability (Dziobek et al., 2006; Ritter et al., 2011). We used the validated French version of the MASC implemented in a Microsoft PowerPoint® presentation (Martinez et al., 2017). In total, the task took about 45 min to complete. Request of access to the French version of the MASC's stimuli should be addressed to Dr Garel, Dr Booij or Dr Herba form the Saint Justine University Hospital in Montreal, Canada.

2.2.2. Neuropsychological and behavioral characteristics of DM1 patients

The DM1 patients were assessed with a comprehensive neurocognitive battery. The intellectual quotient (IQ) was estimated through the administration of four tasks (vocabulary, similitudes, cubes, and matrices) (Gré et al., 2009) from the Weschler Adult Intelligence Scale – Third Edition (Wechsler, 2000) (WAIS-III). Working memory was evaluated with the letter–number sequencing test from the WAIS-III, verbal episodic memory was evaluated with the French version of the Hopkins Verbal Learning Test (Rieu et al., 2006) (total score and delayed recall), and non-verbal episodic memory was evaluated with the 10/36 test (Dujardin et al., 2004) (total score and delayed recall). With regard to instrumental functions, language was evaluated with the naming task from the GRECO neuropsychological semantic battery (Merck et al., 2011) (BECS-GRECO), visuo-constructive abilities were evaluated with the Beery Visual Motor Integration test (Beery & Beery, 2006), and visual gnosis was evaluated with the letter and cube subtests from the Visual Object and Space Perception test battery (Warrington & James, 1991). With regard to executive functions, verbal incitation (GREFEX, 2001) was evaluated with a categorical (the participant was asked to give the names of as many animals as possible in 2 min) and a phonological (the participant was asked to give as many words beginning with the letter "p" as possible in 2 min) fluency tests, mental flexibility was evaluated with the Trail Making Test (Reitan, 1958) (TMT; Trails B – Trails A difference score), and inhibition was evaluated using the D-KEFS (Delis-Kaplan Executive Function System) version (Delis et al., 2001) of the Stroop test (rated as the interference task completion time divided by the naming completion time). Information processing speed was evaluated with the Computerized Speed Cognitive Test (Ruet et al., 2013) (CSCT).

We also evaluated behavioral parameters in DM1 patients. Symptoms of autism spectrum condition were measured with the Autism Spectrum Quotient Test – short form (Allison et al., 2012). Apathy was evaluated on the Lille Apathy Rating Scale (LARS) (Dujardin et al., 2013). Social interactions were assessed with a social functioning questionnaire (*Questionnaire de Fonctionnement Social;* QFS), with subscores evaluating the frequency of the person's involvement in social activities (leisure activities, relationships outside the family, participation in community life, etc.) and the person's satisfaction with their social behaviors (Zanello et al., 2006). Depression and anxiety were evaluated on the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Fatigue was estimated using the Fatigue Severity Scale (Krupp et al., 1989). Lastly, quality of life in four domains (physical health, psychological state, social relationships, and environment) was rated using the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) questionnaire (Baumann et al., 2010).

Tests were administered in 2 sessions (first neurocognitive assessment during approximately 1 h 15 min, then a 20 min break, then the MASC followed by behavioral parameters assessment during approximately 1h15) with the patients' usual visual corrections (eyeglasses, corrective lens), in a place with good lighting. None of the patients had significant visual impairments, and all patients had a regular ophthalmologic follow-up.

Access to most of the cognitive tests and behavioral questionnaires are possible through the publication referred in the manuscript (or by a contact with the main author of the publication). Note that the Weschler Adult Intelligence Scale – Third Edition (WAIS-III), Beery Visual Motor Integration test, Visual Object and Space Perception test battery, and D-KEFS (Delis-Kaplan Executive Function System) battery are under legal copyright restrictions and can be obtained from the copyright holders in the cited references.

2.2.3. *Clinical and laboratory measurements*

The DM1-related parameters considered in the present study were age at symptoms onset, duration of DM1 disease (defined as the time interval between symptoms onset and the neuropsychological evaluation), the severity of muscle involvement evaluated by the MIRS, and the size of the CTG triplets repeat expansion in leukocytes at the time of diagnosis.

2.2.4. *Magnetic resonance imaging*

A 3-T brain MRI was performed in 39 of the 50 DM1 patients (78%) who had no contraindications (e.g. pacemaker, claustrophobia), either another day or after the cognitive and behavioral assessment (see Supplementary data for more information regarding the procedure). We used the volBrain online tool (Manjó et al., 2016) to automatically segment and measure different brain volumes (brain supratentorial volume, supratentorial white matter volume, supratentorial gray matter volume) on 3D-T1 images. ITK-SNAP® software [version 3.6.0, www.itksnap.org (Yushkevich et al., 2006)] was used for the semi-automatic measurement of the volume of white matter hyperintensities on 3D-FLAIR images. To obtain normalized values, all measured volumes were divided by the intracranial volume.

2.3. *Statistics*

We first compared the groups (DM1 patients *vs* controls) with regard to their demographic characteristics (sex; using a chi^2 test; age and educational level, using Student's t-test). We next probed the intergroup difference in the total MASC score, using Student's t-test. We used repeated-measures ANOVA to compare the groups with regard to the types of error (absence of mentalization, hypomentalization, hypermentalization) and the ToM components (affective *vs* cognitive ToM, perceptive *vs* contextual ToM), with the two ToM parameters as within-subject factors and group as the between-subjects factor. Post-hoc tests were conducted in case of a significant interaction, with Tukey's correction. For the scores with significant differences between DM1 patients and controls, we

used a one-tailed Crawford's test (single case method) to compute the percentages of patients with an impairment(-Crawford et al., 2010). Crawford's test allows the comparison of a single subject score to the performance observed in a control population. It helps to determine whether the score obtained by each DM1 patient should be considered as significantly below performance of the control group (one-tailed test was used as we were only interested in identifying DM1 patients who scored below the controls). Using the Crawford procedure on each DM1 patient performance gave the proportion of DM1 patients that were impaired compared to the control group. Lastly, we used linear models to develop an exploratory, non-corrected index of the association between MASC score/subscores/error types on one hand, and demographic characteristics, DM1-related parameters, cognitive, behavioral, social and quality of life scores, and normalized brain volumes on the other hand. Each parameter was entered separately in a model, and then all parameters significantly associated with total MASC score were included in a multivariate model. The threshold for statistical significance was set to $p < .05$. Effect sizes were estimated using Cohen's d, a value of .2 being considered as a small effect size, .5 medium, .8 large and 1.2 very large effect size(Sawilowsky, 2009). All statistical analyses were performed with R software (version 4.0.2), using the afex (https://CRAN.R-project.org/package=afex), emmeans (https://CRAN.R-project.org/package=emmeans) and effectsize packages (Ben-Shachar et al., 2020).

The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the head coordinator of the DMVASCOG study, Dr Céline Tard, Department of neurology, Lille University Hospital (celine.tard@chu-lille.fr). Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must complete a formal data sharing agreement before accessing the data.

3. Results

3.1. Demographic and clinical characteristics

The 50 DM1 patients and the 50 controls did not differ with regard to demographic characteristics (see Table 1). Based on the age at symptoms onset (De Antonio et al., 2016), 13 DM1 patients (26%) had a juvenile form, 22 (44%) an adult form and 15 (30%) a late-onset form (mean ± SD age at symptom onset: 32.1 ± 16.5, range: 10–72; mean DM1 duration: 12.1 ± 9.1 years; range: 1–44 years). The mean CTG triplets repeat expansion size was 431.7 ± 279.1 (range 51–1200). Regarding the severity of muscle impairment, the Muscular Impairment Rating Scale (Mathieu et al., 2001) (MIRS) was 1 for 10% of patients (5/50), 2 for 24% (12/50), 3 for 44% (22/50) and 4 for 22% (11/50). DM1 patients scores for the neuropsychological, behavioral, social and quality of life evaluation are provided in the Supplementary data section (Table 2).

3.2. MASC total score

The mean MASC total score was lower for DM1 patients than for healthy controls ($p < .001$; Fig. 1). Using Crawford's test, we observed a ToM impairment in 19 over 50 DM1 patients (38%), compared to controls.

3.3. Error profiles for MASC total score

The error profiles for the total MASC score differed between DM1 patients and healthy subjects ($p = .015$ for the interaction between groups and error types). DM1 patients presented more hypomentalization errors than controls ($p < .001$), but there was no significant difference regarding the absence of mentalization ($p = .16$) or hypermentalization ($p = .95$) errors. Hypermentalization was more frequent than the absence of mentalization in both DM1 patients ($p < .001$) and controls

Table 1 – Demographic and ToM characteristics of DM1 patients and controls (MASC = Movie for the Assessment of Social Cognition). Statistic tests used to compare DM1 patients and healthy controls were the chi² test for the sex, Student's t-test fo the age, educational level and total MASC score. Repeated-measures ANOVA for the other parameters which were set as within-subject factors and group as the between-subjects factor; presented *p*-values are those for the interaction, main effect, and/or of post-hoc test with Tukey's correction if the interaction term was significant (marked with a *), otherwise we presented *p*-value comparing both group. P-values considered as significant are in bold.

	DM1 (n = 50)	Healthy controls (n = 50)	Statistics
Sex	24 F/26 M	27 F/23 M	X^2 (1) = .16, p = .69
Age (years)	44.18 ± 13.64	41.32 ± 13.92	t(49) = 1.04, p = .30, d = .21
Educational level (years)	11.88 ± 3.21	11.50 ± 3.98	t(94) = .53, p = .60, d = .11
Total MASC score (%)	61.82 ± 10.20%	70.40 ± 6.67%	t(84) = −4.98, **p < .001**, d = 1.1
			Interaction: F(98) = 3.79; **p = .054**
MASC affective subscore (%)	57.5 ± 11.2%	69.1 ± 9.0%	*t(98) = 5.71, **p < .0001**, d = 1.15
MASC cognitive subscore (%)	64.4 ± 15.1%	70.6 ± 10.3%	*t(98) = 2.37, p = .090, d = .48
MASC perceptive subscore (%)	60.9 ± 17.5%	73.8 ± 12.9%	Interaction: F(98) = 1.58, p = .21
			Main effet (group): F(98) = 24.50, **p < .0001**
MASC interpretative subscore (%)	60.9 ± 13.1%	69.9 ± 9.2%	
			Interaction: F(168) = 4.65, **p = .015**
Absence of mentalization errors (%)	6.8 ± 4.8%	4.8% ± 3.3%	*t(98) = .88, p = .16, d = .49
Hypomentalization errors (%)	18.3 ± 8.1%	12.6 ± 5.0%	*t(98) = 4.19, **p = .0008**, d = .85
Hypermentalization errors (%)	13.1 ± 5.7%	12.1 ± 4.9%;	*t(98) = 2.43, p = .95, d = .18

Table 2 – Associations between the total MASC score (%), hypomentalization (%), and the affective subscore (%) and first demographic parameters, then DM1-related parameters. The association with DM1-related parameters were adjusted on age and educational level.

	Total MASC		Hypomentalization		Affective subscore	
	β	p	β	p	β	p
Demographic parameters						
Sex	–	.24	–	.69	–	.24
Age	−.343	**<.001**	.32	**<.0001**	−.17	.14
Educational level	1.19	**<.01**	−.29	.42	1.17	**<.05**
D1-related parameters						
Age at symptom onset	.046	.73	−.112	.31	.446	.69
DM1 duration	−.046	.73	.112	.31	−.446	.69
CTG triplets repeat expansion size	−.012	**.0083**	.005	.19	−.062	.11
Muscular Impairment Rating Scale	−1.023	.45	.530	.64	−14.814	.19

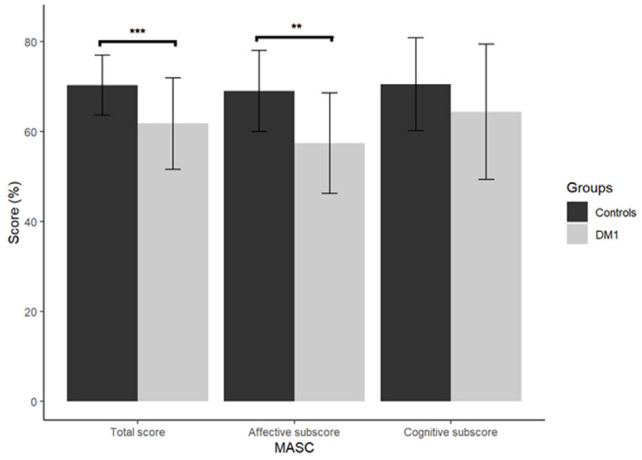

Fig. 1 – The total MASC score and the affective and cognitive subscores (expressed as the proportion of correct answers in %) in controls and in DM1 patients (*$p < .0001$; **$p < .001$; *$p < .01$).**

($p < .001$), and hypomentalization was more frequent than hypermentalization in DM1 patients ($p < .01$) but not in controls ($p = 1.0$).

3.4. *Affective and cognitive MASC subscores*

We observed a non-significant trend ($p = .054$) for the interaction between the groups and the affective/cognitive subscores. As the p-value was close to the significance threshold, we chose to perform pairwise comparisons between DM1 patients and controls. The affective subscore was significantly lower among DM1 patients than among controls ($p < .001$) whereas there was no difference regarding the cognitive subscore ($p = .09$). DM1 patients displayed significantly lower affective than cognitive subscores ($p < .01$), whereas there was no significant difference among controls ($p = .88$).

Using Crawford's test, 25 (50%) of our 50 DM1 patients had an affective ToM impairment, whereas only 10 (20%) had an impairment in cognitive ToM. The most common ToM profile was an impairment in affective ToM alone in 16 patients (32%), followed by an impairment in both affective and cognitive ToM in 9 patients (18%) and lastly an impairment in cognitive ToM alone in only one patient (2%).

The error profile for affective ToM was different between DM1 and controls ($p = .008$ for the interaction between the group and the type of error): DM1 patients presented more frequent hypomentalization ($p < .01$) and absence of mentalization ($p < .01$) than controls, whereas there was no significant difference for hypermentalization ($p = 1.0$). The error profile for cognitive ToM was not significantly different between DM1 patients and controls ($p = .23$ for the interaction term).

3.5. *Perceptive and contextual MASC subscores*

We observed no interaction between the group and the perceptive/interpretative subscores ($p = .21$). Only a group effect was observed with DM1 patients displaying significantly lower subscores for both perceptive and contextual items than controls ($p < .001$).

3.6. *Predictors of MASC performance in DM1 patients*

Sex was not significantly associated with any of the MASC scores (all p-values > .05). Age was significantly associated with a lower total MASC score ($\beta = -.34$; $p < .001$; $R^2 = .20$), and more hypomentalization errors ($\beta = .32$; $p < .0001$; $R^2 = .27$) but did not significantly impact the affective subscore ($\beta = -.17$; $p = .14$; $R^2 = .02$). A lower educational level was significantly associated with a lower total MASC score ($\beta = 1.19$; $p < .01$; $R^2 = .12$) and a lower affective subscore ($\beta = 1.17$; $p < .05$; $R^2 = .09$), but was not associated with the frequency of hypomentalization errors ($\beta = -.29$; $p > .05$; $R^2 = .00$).

We next built linear models to explain the social cognition impairment observed in DM1 (total MASC score, frequency of hypomentalization errors and affective subscore) with the specific characteristics of DM1 patients (disease characteristics, cognitive function, behavioral manifestations, and MRI brain volumes). Given that age and educational level were associated with MASC scores, we adjusted our linear models for these parameters.

When considering the patients' clinical and laboratory characteristics, we observed that a larger CTG triplets repeat expansion was significantly associated with a lower total MASC score ($\beta = -.01$; $p < .01$; $R^2 = .40$); however, the associations with the affective subscore and hypomentalization were not significant (Table 2). The other parameters related to

Table 3 – Associations between normalized MRI brain volumes and the total MASC score (%), hypomentalization (%), and the affective subscore (%).

	Total MASC		Hypomentalization		Affective subscore	
	β	p	β	p	β	p
Supratentorial brain volume (%)	.924	.0680	−.717	.084	10.051	**.0181**
Supratentorial white matter (%)	1.715	**.0455**	−.648	.37	6.019	.42
Supratentorial gray matter (%)	.369	.50	−.549	.22	8.872	.0508
White matter hyperintensity (%)	−3.295	.31	.680	.80	−26.290	.34

DM1 (age symptom onset, DM1 duration and the MIRS score) were not significantly associated with any of the ToM scores.

With regard to cognitive function, a higher total MASC score was only associated with a faster information processing speed (CSCT score; $\beta = .15$; $p < .05$; $R^2 = .36$). The MASC scores were not associated with the IQ or the behavioral, social and quality of life scores (Supplementary data, Table 2).

For the brain volumes (Table 3), the total MASC score was positively associated with the normalized supratentorial white matter volume ($\beta = .77$; $p < .05$; $R^2 = .43$), and the affective subscore was positively associated with the normalized supratentorial brain volume ($\beta = 1.51$; $p < .05$; $R^2 = .18$).

We included in a single multivariate linear model parameters significantly associated with total MASC score, first excluding MRI parameters to include all 50 DM1 patients. Total MASC score remained significantly associated with CTG triplets' expansion size, CSCT score and age but not educational level (Table 4). We then included supratentorial white matter volume (%) in the model on the 39 patients who performed a brain MRI; only the CTG triplets repeat expansion size variable remained significantly associated with the total MASC score.

4. Discussion

We used the MASC to explore ToM in DM1 patients. This tool enabled us to differentiate between affective and cognitive ToM components and to obtain a qualitative analysis of the error profile. Our present results confirmed that DM1 patients have impaired ToM abilities (Kobayakawa et al., 2012; Serra et al., 2016, 2020), showing a significant difference compared to controls in the total MASC score (with a large effect size). This impairment was mainly explained by patients' difficulties to recruit ToM processes as hypomentalization errors were more frequent in this group than in controls. More specifically, DM1 patients were particularly impaired for affective ToM, with 50% of them showing impairment in performance relative to controls. There was no significant difference regarding cognitive ToM in DM1 patients compared to controls, and their error profiles did not differ from controls for these latter situations. Moreover, impairments of DM1 patients do not seem to be driven by specific difficulties to analyze perceptive stimuli over contextual information. This favors the idea of a primary and specific impairment of ToM, rather than the hypothesis that ToM impairment in DM1 might be secondary to a defect of perception of social cues (such as emotion recognition) (Labayru et al., 2018).

Table 4 – Multivariate linear models explaining the total MASC score, first excluding supratentorial white matter, then including it.

	Total MASC		Adjusted R^2
	β	p	
First model: excluding MRI (n = 50)			
CTG triplets repeat expansion size	−.013	**.007**	
CSCT	.404	**.014**	.45
Age	−.246	**.037**	
Education level	.560	.21	
Second model: including MRI (n = 39)			
CTG triplets repeat expansion size	−.011	**.034**	
CSCT	.343	.051	
Age	−.230	.10	.51
Education level	.785	.12	
Supratentorial white matter	1.619	.06	

Our results indicate that the ToM impairment in DM1 mainly concerns affective processes. This view is strengthened by the spectrum of severity of ToM impairment we found within the DM1 population: the affective ToM component alone might be affected in milder ToM impairment, whereas both affective and cognitive components might be affected in more severe forms. Whether a given patient may evolve within this spectrum over time and whether this ToM impairment may progress remains unknown. Longitudinal studies are required to disentangle an eventual inherent ToM involvement from a progressive impairment of ToM as DM1 progresses. In this respect, it is noteworthy that we did not find any association between ToM performances and the patient's disease duration. Furthermore, we also found no association between ToM and age at DM1 symptoms onset. As ToM matures during adolescence and one-fourth of our patients had a juvenile onset of DM1, our results do not specifically point toward a neurodevelopmental origin of ToM involvement in DM1. A preferential involvement of affective over cognitive ToM have been demonstrated in other diseases, such as mild-stage behavioral variant frontotemporal dementia (Torralva et al., 2015), whereas other neurodegenerative such as Alzheimer's disease (Laisney et al., 2013) or multiple sclerosis (Isernia et al., 2019) might preferentially disturbed cognitive ToM. Moreover, ToM deficits have been associated with executive functions disorders in other diseases such as Parkinson's disease (Maggi et al., 2022) or Alzheimer's disease (Laisney et al., 2013) while we did not observe such an association in DM1 patients. This also argues for a specific impairment of theses abilities in DM1.

From a qualitative point of view, we observed a ToM error profile for DM1 patients characterized by more hypomentalizations than controls while the two groups did not differ for

other error types. Therefore, ToM impairment in DM1 seems to have a particular nature, differing from other conditions, such as borderline personality disorder in which errors are predominantly hypermentalizations (Sharp et al., 2011). When considering only affective ToM, we confirm that more hypomentalizations were made, but we also even found more errors reflecting the absence of mentalization (while there was still no difference regarding hypermentalization). Both hypomentalization and the absence of mentalization errors sign a deficit in the recruitment of ToM abilities (Lahera et al., 2014). The absence of mentalization is the most severe form of "inframentalization" as it reveals a complete lack of ToM processing in the understanding of a situation, and this was more frequently observed in DM1 patients than controls when affective inferences were to be made. This again argues for a more specific impairment of affective ToM in DM1 patients as recruitment of ToM may even be impossible in these situations. This particular ToM impairment profile may thus give rise to particular manifestations in interpersonal relationships and might be associated with disturbances in specific brain networks, which should be investigated in future studies.

To explore the potential determinants and consequences of these ToM impairments in DM1, we performed an exploratory analysis and found associations with CTG triplets repeat expansion size, brain MRI volumes and information processing speed. The patients' CTG triplets repeat expansion size was the only DM1-related characteristic with an impact on ToM performances, and the only parameter remaining significantly associated with total MASC score on a single-multivariate model. CTG triplets repeat expansion size has often been linked to the severity of the clinical manifestations of DM1 (Thornton, 2014) and several studies (Serra et al., 2016, 2020; Winblad et al., 2006) have found a significant relationship with impairment in social cognition. The present study found that 40% of the variance in the total MASC score could be accounted for by this genetic factor. This might indicate that ToM impairment are inherently related to DM1 disease. As mentioned above, no other clinical characteristics that reflect the severity of the disease (e.g., age at disease onset or the severity of muscle-related symptoms) were significantly associated with ToM performances, contrary to previous observations (Serra et al., 2016, 2020; Winblad et al., 2006). Moreover, brain volume differences were predictive of MASC scores; more specifically, the white matter volume was predictive of the total MASC score. These associations are significant but relatively weak, probably because the brain measures used in our study are only a rough reflection of the changes within specific neural networks involved in ToM (Serra et al., 2016), that might be affected in DM1 patients. Indeed, associations have been observed in DM1 patients between ToM abilities and abnormal functional connectivity within a specific brain network involving multiple cortical areas joigned by different white matter tracks (Serra et al., 2016). More precise studies about structural and functional brain connectivity may give further information.

Alternatively, we could not completely rule out contributions of other indirect factors to ToM performance in DM1 patients, and notably information processing speed, which was the only cognitive factor associated with poor MASC performance. Information processing speed has frequently been linked to poorer performance in ToM tasks [e.g. in healthy volunteers (Laillier et al., 2019)] and might be considered as a worsening factor of ToM abilities in DM1. An in-depth investigation of these relationships is however warranted as another explanation might be that the white matter disturbances observed in DM1 may be the common cause of both information processing speed (Wozniak et al., 2014) and ToM impairments, explaining the associations between these two cognitive abilities. In our study, IQ, reflecting intellectual abilities, was not associated with ToM performance, unlike previous results from a study (Labayru et al., 2018) but this latter excluded patients with an IQ below the normal range (i.e., below 85) while we only excluded patients with more severe intellectual disabilities (an IQ below 70). Note that we still showed no association with IQ when we only considered DM1 patients from our study who had an IQ over 85 ($n = 23$).

Taken as a whole, this study contributes to the current debate on the variables that underlie ToM impairments in DM1 patients: some researchers consider that these impairments result from more general cognitive difficulties (Labayru et al., 2018) or physical handicap (Bird et al., 1983), whereas others consider that a DM1-related brain impairment has a direct impact on social cognition (Kobayakawa et al., 2012; Serra et al., 2016, 2020). Our results give some support to the latter hypothesis, as ToM performance was associated with CTG triplets repeat expansion and with brain volumes on MRI.

No associations between ToM performance and behavioral manifestations were found in DM1 patients. We expected more specifically to observe a relationship between ToM abilities and the social functioning of our patients, as observed in other clinical populations (Bishop-Fitzpatrick et al., 2017). Data in the literature on the relationships between the MASC and behavioral, social and quality of life measures are scarce and sometimes contradictory. Depressive scores were correlated with absence of mentalization errors in affective ToM in patients with depressive disorders (Wolkenstein et al., 2011), and hypomentalization errors were correlated with distress scale during the task in subjects with high social anxiety (Lenton-Brym et al., 2018). However, the MASC performance was not associated with depression scores in early stage of multiple sclerosis (Kraemer et al., 2013), neither with depression and anxiety scores in adolescent girls (Porter-Vignola et al., 2022) nor in anorexia nervosa (Brockmeyer et al., 2016). Significant correlations have been observed between the MASC performance and social behavior disorders in patients with traumatic brain injury and healthy subjects, but specific behavior disturbances were also correlated only in one of these groups but not in the other, as for example reduction of activities, apathy, was correlated to MASC score in traumatic brain injury group but not in healthy subjects (Allain et al., 2019). In patients with focal epilepsy, MASC errors were associated with social integration, more precisely loneliness (Metternich et al., 2022). To our knowledge, there is no data about associations between the MASC and quality of life measures. One explanation for the lack of association between ToM and behavioral measures in our patients might be that the autoquestionnaire used in this study lacks sensitivity to capture the specific disturbances of DM1 patients in

interpersonal relationships. More specific social cognitive functioning scales (such as measures of empathy) might be considered in future studies assessing the consequences of the ToM impairment observed in DM1 patients. Note that Labayru et al. (2018) administered an empathy questionnaire to DM1 patients but did not find any differences between DM1 patients and controls. This questionnaire was however a self-report of these abilities, as it was the case for the questionnaires in our study. Self-report questionnaires require adequate introspection and self-assessment capacities, which might be compromised in DM1 patients. Information about social functioning provided by a healthy close relative (not affected by DM1) or role-playing tasks might thus be more suitable for assessing social functioning and should be considered in future research.

Our study has some limits. As our work was exploratory, we performed multiple comparisons without correction and so cannot rule out false-positive findings. Among significant results, we found an association between CTG triplets number and the total MASC score. The CTG expansion size can vary with time (Martorell et al., 1998) and was only measured at diagnosis and not close to the neuropsychological assessment, therefore the CTG associations could have changed if the measure would have been repeated. Moreover, the CTG expansion size might differ in the leucocytes than in the brain (Sergeant et al., 2001), and the latter measure might be a better reflection of how DM1 pathology affects the brain. However, brain CTG quantification is only possible on brain samples, obtained from post-mortem examination or invasive brain biopsies. Finally, in view of the study's design, the relationships highlighted are not necessarily causal but are used to generate hypotheses that might help to guide future studies.

5. Conclusion

This study provides original evidence that ToM impairment in DM1 is mainly related to the poor recruitment of ToM processes (hypomentalization), concerns affective ToM more than cognitive ToM, and is not driven by a defect of social cues perception. Exploratory analyses indicated that this ToM impairment is associated with information processing speed (but not with global intelligence) and also with CTG expansion size and imaging parameters. This indicates that ToM impairment is at least partly secondary to DM1-related brain abnormalities, rather than being only explained by the impairment of other neurocognitive and behavioral functions. This characterization of the ToM profile in DM1 will be useful for future studies using advanced imaging techniques (quantitative MRI, functional/anatomical connectivity) which may explain this ToM profile by the preferential involvement of specific brain networks. Our findings may also guide the provision of neurological, psychological, and social support to DM1 patients, with rehabilitation focusing on the affective aspects of ToM to prevent interpersonal relationship problems. Longitudinal studies are needed to determine whether the disturbance in social cognition is stable or progressive in time, which might provide clues to the possible neurodegenerative or neurodevelopmental nature of this cognitive impairment.

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Grégory Kuchcinski, Loren Fragoso, Amina Wilu-Wilu: Investigation.

Pierre Maurage: Methodology; Investigation; Writing – review & editing.

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Declaration of competing interest

The authors have no disclosures to report.

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Supplementary data

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