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Executive Dysfunction, Social Cognition Impairment, and Gray Matter Pathology in Myotonic Dystrophy Type 2: A Pilot Study

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Running head: Executive Dysfunction and GM Changes in DM2

Abstract

Background: In contrast to myotonic dystrophy type 1, the cognitive and radiologic profile of myotonic dystrophy type 2 (DM2) is relatively poorly characterized.

Objective: To conduct a pilot study to systematically evaluate cognitive and radiologic features in a cohort of Greek individuals with DM2.

Method: Eleven genetically confirmed individuals with DM2 and 26 age- and education-matched healthy controls (HC) were administered the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) to screen for impairment in multiple cognitive domains. MRI data were evaluated by morphometric analyses to identify disease-specific gray and white matter alterations. The following statistical thresholds were used for cognitive comparisons: $P_{FDR} < 0.05$ and Bayes factor (BF_{10}) > 10.

Results: The DM2 group exhibited cognitive impairment (ECAS Total score; $P_{FDR} = 0.001$; $BF_{10} = 108.887$), which was dominated by executive impairment ($P_{FDR} = 0.003$; $BF_{10} = 25.330$). A trend toward verbal fluency impairment was also identified. No significant impairments in memory, language, or visuospatial function were captured. The analysis of subscores revealed severe impairments in social cognition and alternation. Voxel-based morphometry identified widespread frontal, occipital, and subcortical gray matter atrophy, including the left superior medial frontal gyrus, right medial orbitofrontal gyrus, right operculum, right precuneus, bilateral fusiform gyri, and bilateral thalami.

Conclusion: DM2 may be associated with multifocal cortical and thalamic atrophy, which is likely to underpin the range of cognitive manifestations mostly characterized by executive impairment and specifically by impaired social cognition.

Key Words: myotonic dystrophy type 2, cognitive impairment, executive impairment, social cognition, voxel-based morphometry

Abbreviations

BF = Bayes factor. **DM** = myotonic dystrophy. **DM1** = myotonic dystrophy type 1. **DM2** = myotonic dystrophy type 2. **ECAS** = Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen. **FDR** = false discovery rate. **FWE** = family-wise error. **GM** = gray matter. **HC** = healthy controls. **WM** = white matter.

INTRODUCTION

Myotonic dystrophy (DM) is a multisystem autosomal-dominant condition—the most common form of muscular dystrophy in adults (Harley et al, 1992). Common symptoms of DM include muscle weakness, myotonia, early onset cataracts, insulin resistance, conduction abnormalities, and cognitive changes (Udd and Krahe, 2012). There are two types of DM—DM type 1 (DM1) and DM type 2 (DM2)—which share many common features, although they have striking differences (Meola and Cardani, 2015). *DM1* is caused by expansion of a CTG triplet repeat in the 3 prime untranslated region of the DM protein kinase gene on chromosome 19q13.3; *DM2* is caused by expansion of a CCTG tetranucleotide repeat in the first intron of the nucleic acid binding protein gene on chromosome 3q21 (Yum et al, 2017). DM1 has an incidence of ~1:8000; the exact frequency of DM2 is not yet known due to a lack of epidemiological data, although it seems that there are great differences among different geographic areas, and in some countries, it is probably as common as DM1 (Meola and Cardani, 2015).

DM1 has been investigated extensively with regard to cognitive impairments and cerebral changes, but the literature regarding DM2 is sparse in that regard. The few available DM2 studies have identified executive impairment (eg, decision-making, planning, divided attention and attentional control, interference, alertness with and without warning signal, verbal fluency with change of categories, conceptual reasoning, set shifting, working memory),

impaired episodic memory (eg, verbal and nonverbal short-term memory, verbal learning, verbal and visuospatial long-term memory), and impaired visuospatial functions (eg, spatial visualization ability, visuospatial/constructional dexterity) as cognitive impairments (Meola et al, 2003; Peric et al, 2017b), but existing studies are inconsistent due to differences in the neuropsychological domains that they assessed (Theodosiou et al, 2021).

Cerebral alterations have been previously described in individuals with DM2 (Gourdon and Meola, 2017), but the alterations have been thought to be less extensive than in individuals with DM1. Structural imaging studies of individuals with DM2 have mostly captured widespread cortical and subcortical gray matter (GM) atrophy (specifically in the frontal and parietal regions and the brainstem, as well as in the hypothalamus, thalamus, and hippocampus) and white matter (WM) degeneration in commissural, association, and projection tracts (mostly in the corpus callosum, internal and external capsules, fornix, and cingulate bundle) (Minnerop et al, 2018). Very few DM2 studies have adopted a multimodal approach to study CNS involvement using a standardized neuropsychological and radiologic protocol (Gourdon and Meola, 2017).

Although the ascertainment of cognitive changes in individual patients may have important ramifications for multidisciplinary management, formal neuropsychological testing often is not available, and no DM-specific neuropsychological screening tools currently exist (Theodosiou et al, 2021). More broadly, the characterization of DM2-associated cognitive profiles may have implications for guideline development, planning of multidisciplinary interventions, and generation of best practice recommendations. Previous Greek cohort studies (Papadimas et al, 2015; Papadopoulos et al, 2018) and case reports (Karatzikou et al, 2018) have not characterized DM2-associated cognitive functions or GM and WM degeneration.

Considering the paucity of radiologically supported neuropsychological studies of individuals with DM2, we aimed to conduct a pilot study to systematically evaluate cognitive

and radiologic features in a cohort of Greek individuals with DM2 using a multidomain neuropsychological screening instrument that may prove useful in routine clinical practice with accompanying neuroimaging. In clinical practice, comprehensive neuropsychological testing by a qualified neuropsychologist is seldom available; therefore, sensitive multidomain screening instruments are of pragmatic value (Bigler, 2017). Considering the most recent review regarding the profile of cognitive impairment in individuals with DM2 (Theodosiou et al, 2021), we hypothesized that Greek individuals with DM2 would show cognitive impairment that will be more prominent on executive functions and further show brain changes with a characteristic pattern of frontal pathology.

METHOD

Participants

Over a 10-month period, we recruited adults with genetically confirmed DM2 and demographically related healthy controls (HC) to participate in our study. The individuals with DM2 had visited the specialized outpatient neuromuscular clinic at Aeginition Hospital in Athens, Greece; had been examined thoroughly; and had undergone electrophysiological assessment, including nerve conduction studies and needle electromyography. Laboratory tests were also carried out. Peripheral blood was obtained from all of the individuals who had been referred for genetic testing after informed consent, and genetic analysis was performed as described previously (Papadimas et al, 2015). The HC were recruited by word of mouth.

Study inclusion criteria included genetic confirmation of DM2 (only for patients), age <75 years, Greek as the native language, and education >3 years. Exclusion criteria included comorbid neurologic (other than DM2 for patients) and psychiatric (eg, schizophrenia, major depressive disorder, bipolar disorder) conditions, alcohol or substance abuse, and sensory impairment.

The study protocol was approved by the Aeginition Hospital Institutional Ethics Committee and was performed according to the ethical guidelines of the Declaration of Helsinki and its later amendments. All individuals provided informed written consent before enrolling in the study.

Cognitive Evaluation

The same neuropsychologist (T.T.) administered all of the cognitive tests in the exact same order on the same day so as not to have any discrepancies in the participants' evaluations. All cognitive tests were standardized in the Greek language and local population. The cognitive tests included the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS; Abrahams et al, 2014; Kourtesis et al, 2020), the Mini-Mental State Examination (Mougias et al, 2020), and the Hospital Anxiety and Depression Scale (Michopoulos et al, 2008). The duration of the cognitive evaluation was 30–45 minutes.

The ECAS is a brief multidimensional scale that assesses executive functions (eg, working memory, social cognition, inhibition, alternation), verbal fluency, memory (immediate recall, delayed recall, retention), language, and visuospatial functions (eg, simple and composite visuospatial organization and planning). It was originally developed for individuals with amyotrophic lateral sclerosis but has been used with individuals with other neurodegenerative conditions (Foley et al, 2018). The psychometric properties of the ECAS in individuals with DM2 have been previously examined (Theodosiou et al, 2018).

Neuroimaging Acquisition and Analysis

Three-dimensional T1-weighted neuroimaging data were acquired for 10 individuals with DM2 and 17 HC using a 3T Philips scanner with a repetition time of 9.9 ms, echo time of 3.7 ms, and isometric voxel-size of 1 mm^3. The 3D T1-weighted sequence was acquired as part of a comprehensive neuroimaging protocol lasting ~35 minutes. MRI was not performed with one individual who had metal implants that were incompatible with the MRI scanner.

With regard to the HC group, MRI data were not available for 9 of the 26 participants due to metal implants (n = 3), claustrophobia (n = 2), denial to participate (n = 1) or to complete the protocol (n = 1), and motion artifacts (n = 2).

The T1-weighted images were analyzed with the computational anatomy toolbox of Statistical Parametric Mapping (SPM12) using MATLAB R2015b. All images were normalized in MNI (Montreal Neurological Institute) space using the default International Consortium for Brain Mapping template before tissue-type segmentation. The normalized modulated GM and WM images were smoothed with an 8-mm full-width-at-half-maximum isotropic Gaussian kernel.

Statistical Analysis

We used independent samples *t* tests to compare the ECAS subscores of the individuals with DM2 with those of the HC following corrections for multiple comparisons based on false discovery rate (FDR). The following statistical thresholds were used: $P_{FDR} < 0.05$ and Bayes factor (BF_{10}) >10 (Lee and Wagenmakers, 2013). If $1 < BF_{10} < 3$, then BF_{10} indicates *anecdotal* evidence in favor of H_1 over H_0; if $3 < BF_{10} < 10$, then BF_{10} indicates *moderate* evidence; if $10 < BF_{10} < 30$, then BF_{10} indicates *strong* evidence; and $BF_{10} > 30$ indicates *very strong* evidence.

In addition to group-based analyses, we used the available normative values for the ECAS (Kourtesis et al, 2020), considered a cutoff score of 2 SDs, and estimated the percentage of individuals with DM2 with preserved or impaired performance on the ECAS Total score and separate cognitive domains. The analyses of demographic and cognitive data were conducted using JASP computer software. Group differences between the individuals with DM2 and the HC in GM and WM density were examined using SPM12, with age, gender, and total intracranial volume as covariates and the statistical threshold set at $P < 0.05$, family-wise error (FWE) corrected.

RESULTS

Participant Demographics and Clinical Data

Initially, 20 individuals with genetically confirmed DM2 agreed to participate in the study. However, nine of the individuals did not participate due to various reasons: a different native language (n = 1), denial to participate (n = 2), living in a different city (n = 1), age >75 years (n = 2), and education <3 years (n = 3). This left us with 11 genetically confirmed individuals with DM2 and 26 HC.

The demographic characteristics of both groups, and the clinical profile of the individuals with DM2, are presented in Table 1. The two groups did not differ in age ($P = 0.392$), gender ($P = 0.860$), education ($P = 0.114$), or mental ($P = 0.129$) or mood ($P = 0.151$) status.

TABLE 1. Demographic and Psychometric Characteristics of the DM2 and HC Groups and Clinical Characteristics of the DM2 Group

Characteristic	**DM2 Group (n = 11)**	**HC (n = 26)**	***P***
Age (years)	61.7 ± 11.0	58.7 ± 9.1	0.392
Gender (male/female)	5/6	11/15	0.860
Education (years)	9.4 ± 3.9	11.4 ± 3.1	0.114
MMSE score	27.36 ± 1.57	28.15 ± 1.35	0.129
HADS score	10.73 ± 8.45	6.69 ± 3.03	0.151
Disease duration (years)	14.7 ± 9.1	–	–

Values are presented as M ± SD unless noted otherwise.

DM2 = myotonic dystrophy type 2. **HADS** = Hospital Anxiety and Depression Scale. **HC** = healthy controls. **MMSE** = Mini-Mental State Examination.

Cognitive Performance

Based on the available normative data (Kourtesis et al, 2020), 73% of our DM2 group fell within the impaired range of performance based on their ECAS Total scores, 55% fell within the impaired range based on their Executive Function subscores, 45% based on their Verbal Fluency subscores, 27% based on their Memory subscores, 18% based on their Visuospatial Functions subscores, and 9% based on their Language subscores. None of the HC fell within the impaired range of performance based on their ECAS Total scores or sub-scores. Significant intergroup differences were identified on both the ECAS Total score (P_{FDR} = 0.001; BF_{10} =108.887; |d| = 1.49) and its subscores (Table 2).

TABLE 2. Cognitive Performance (Raw Scores) and Between-group Differences

ECAS Score	**DM2 Group (n = 11)**	**HC (n = 26)**	$P_{uncorrected}$	P_{FDR}†	BF_{10}†	**Cohen's |d|‡**
Total	88.45 ± 17.22	106.73 ± 9.64	<0.001	**0.001**	**108.887**	1.49
Executive Functions	27.82 ± 7.77	36.12 ± 5.62	0.001	**0.003**	**25.330**	1.32
Working Memory	5.00 ± 1.48	6.31 ± 2.43	0.107	0.143	0.946	0.59
Social Cognition	7.73 ± 2.20	10.42 ± 2.27	0.002	**0.006**	**17.264**	1.20
Inhibition	7.46 ± 4.13	8.27 ± 2.03	0.424	0.424	0.362	0.29
Alternation	7.64 ± 4.61	11.12 ± 2.10	0.003	**0.006**	**11.514**	1.15
Verbal Fluency	13.82 ± 5.55	17.77 ± 3.68	0.015	0.023	3.683	0.92
Memory	12.64 ± 6.50	16.77 ± 3.36	0.015	0.023	2.035	0.92
Language	23.36 ± 2.50	24.65 ± 2.37	0.145	0.145	0.992	0.54
Visuospatial Functions	10.82 ± 1.40	11.42 ± 0.81	0.106	0.123	0.953	0.60

Values are presented as M ± SD unless noted otherwise.

†The following thresholds (bold P_{FDR} and BF_{10} values) were considered for statistically significant differences between the DM2 group and the HC: $P_{FDR} < 0.05$ and $BF_{10} > 10$. If $1 < BF_{10} < 3$, then BF_{10} indicates *anecdotal* evidence; $3 < BF_{10} < 10$, *moderate* evidence; $10 < BF_{10} < 30$, *strong* evidence; and $BF_{10} > 30$, *very strong* evidence.

‡Effect size (Cohen's d) was calculated for between-group differences using the following convention: large effect size: 0.20; medium effect size: 0.50; small effect size: 0.80.

BF = Bayes factor. **DM2** = myotonic dystrophy type 2. **ECAS** = Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen. **FDR** = false discovery rate. **HC** = healthy controls.

Significant executive impairment was identified in the DM2 group (P_{FDR} = 0.003; BF_{10} = 25.330; |d| = 1.32), and a trend toward significance (P_{FDR} < 0.05 and 3 < BF_{10} >10) was identified in verbal fluency (P_{FDR} = 0.023; BF_{10} = 3.683; |d| = 0.92). There were no significant differences in memory (P_{FDR} = 0.023; BF_{10} = 2.035; |d| = 0.92), language (P_{FDR} = 0.145; BF_{10} = 0.992; |d| = 0.54), or visuospatial functions (P_{FDR} = 0.123; BF_{10} = 0.953; |d| = 0.60). Based on the selective involvement of specific subdomains, we further evaluated specific executive functions. The DM2 group scored significantly lower than the HC on the Social Cognition (P = 0.006; BF_{10} = 17.264; |d| = 1.20) and Alternation subtests (P_{FDR} = 0.006; BF_{10} = 11.514; |d| = 1.15). We did not find significant associations between the DM2 group's cognitive scores and their clinical variables (disease duration, Medical Research Counseling Scale (Medical Research Council, 1981), Hospital Anxiety and Depression Scale) (P_{FDR} > 0.05).

GM and WM Density: Between-group Differences

Table 3 lists the regions of the brain that showed significant differences in GM density between the DM2 and HC groups (P_{FWE} < 0.05).

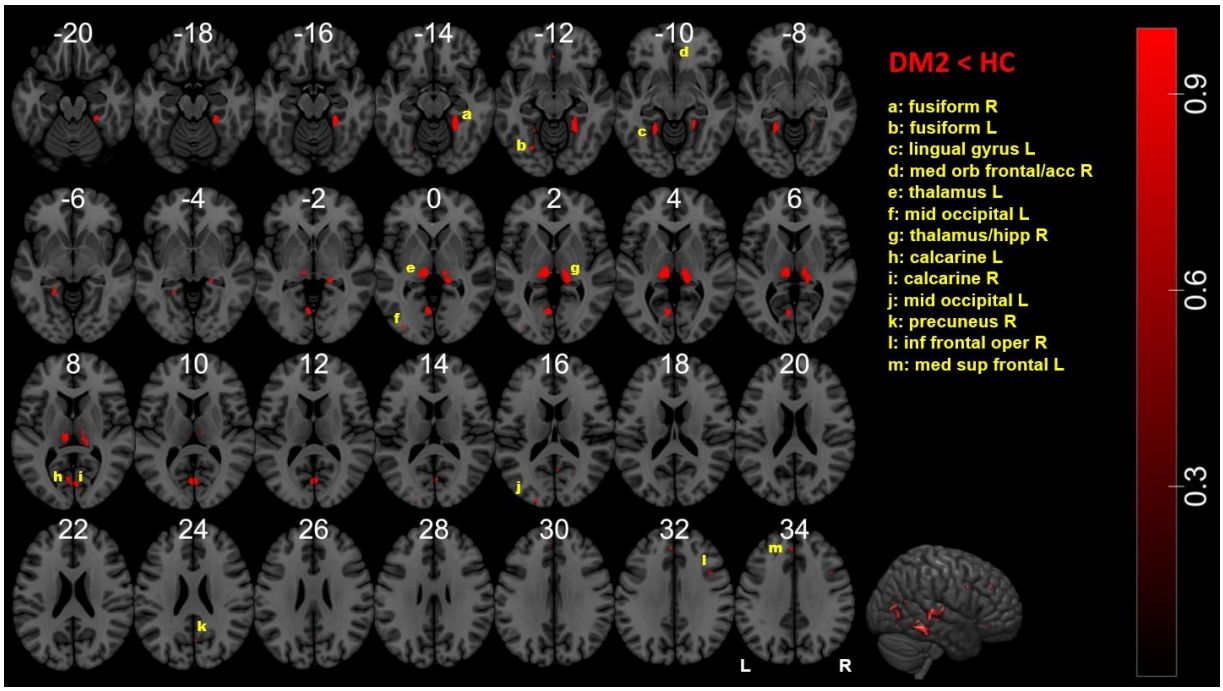
TABLE 3. Brain Regions With Significant GM Density Changes Between DM2 Group and HC

Anatomical Label		Hemisphere	MNI coordinates SPM (x, y, z)	Statistic		
				P_{FWE}	*t*	Voxels
DM2 < HC						
Frontal lobe						
	Medial superior frontal gyrus	Left	–3, 38, 33	0.007	6.94	21
	Inferior frontal operculum	Right	44, 11, 33	0.013	6.68	12
	Medial orbitofrontal gyrus/anterior cingulate gyrus	Right	–2, 36, 11	0.022	6.52	6
Parietal lobe						
	Precuneus	Right	3, –66, 24	0.024	6.57	5
Occipital lobe						
	Fusiform gyrus	Right	24, –41, –15	<0.001	10.34	238
		Left	–26, –71, –12	0.013	6.86	12
	Lingual gyrus/calcarine	Left	–6, –68, 0	<0.001	7.97	275
			–21, –47, –8	<0.001	7.90	108
	Middle occipital gyrus	Left	–36, –87, 0	0.016	7.16	10
	Calcarine gyrus	Right	5, –60, 15	0.024	6.50	5
	Subcortical nuclei	Left	–21, –96, 17	0.016	6.77	10
	Thalamus	Left	–12, –23, 0	<0.001	8.48	314
		Right	15, –35, 3	<0.001	7.34	304

Significant clusters are reported at $P < 0.05$ FWE-corrected for multiple comparisons with a minimum cluster size of five voxels.
DM2 = myotonic dystrophy type 2. **FWE** = family-wise error. **GM** = gray matter. **HC** = healthy controls. **MNI** = Montreal Neurological Institute. **SPM** = Statistical Parametric Mapping.

The DM2 group exhibited significant widespread multifocal GM atrophy, including the bilateral fusiform gyri, left lingual gyrus, left middle occipital gyrus, left superior medial frontal gyrus, and bilateral calcarine gyri, as well as the right inferior frontal operculum, right precuneus, and right anterior cingulate. Bithalamic changes were also detected (Figure 1). We did not find clusters with statistically significant WM alterations in the DM2 group compared with the HC at $P < 0.05$ FWE.

FIGURE 1. Whole-brain voxel-based morphometry analysis revealing GM density changes in individuals with DM2 compared with HC.



Colored clusters are overlaid on the MNI standard brain and show regions with decreased GM density in DM2, significant at $P < 0.05$ (FWE-corrected). **acc** = anterior cingulate cortex. **DM2** = myotonic dystrophy type 2. **FWE** = family-wise error. **GM** = gray matter. **HC** = healthy controls. **hipp** = hippocampus. **inf** = inferior. **med** = medial. **mid** = middle. **MNI** = Montreal Neurological Institute. **oper** = operculum. **orb** = orbital. **sup** = superior.

DISCUSSION

We sought to explore the cognitive and radiologic profile of individuals with DM2 using a standardized clinicoradiological protocol. In line with our hypothesis, we found multifocal cortical and thalamic atrophy, which is likely to underpin the range of observed cognitive manifestations in our DM2 cohort, mostly characterized by executive impairment and specifically by impaired social cognition and alternation. Cognitive impairment is widely recognized in individuals with DM1 and seems to exhibit different profiles depending on symptoms onset (Bajrami et al, 2017; Baldanzi et al, 2016; Cabada et al, 2017; Gaul et al, 2006; Meola et al, 2003; Modoni et al, 2008; Peric et al, 2017b; Zalonis et al, 2010). In contrast,

there is a paucity of neuropsychological studies of individuals with DM2 (Theodosiou et al, 2021).

Cognitive Findings

In our study, a significant proportion of the DM2 group (73%) demonstrated cognitive impairment based on their ECAS Total score. We identified a specific pattern of cognitive impairment in the DM2 group, affecting specific domains and sparing others. Executive impairment with accompanied frontostriatal dysfunction has been consistently described in DM2 studies based on a variety of neuropsychological measures appraising different executive processes (Chen et al, 2018; Gaul et al, 2006; Minnerop et al, 2011; Peric et al, 2015, 2017a, 2017b; Radovanović et al, 2016; Romeo et al, 2010).

The executive functions are the most cited facet of cognitive impairment in individuals with DM2. These individuals typically exhibit impaired performance on neuropsychological tests of executive functions, including the copy form of the Rey-Osterrieth Complex Figure Test, the Wisconsin Card Sorting Test, the Stroop Neuropsychological Screening, semantic and phonemic fluency tasks, the Tower of London Test, the Conditional Associative-Learning measure, the Iowa gambling task, the Trail-Making Test, and executive subtests of the Cambridge Neuropsychological Test Automated Battery (for a detailed review on executive impairment on DM2, please see Theodosiou et al [2021]; for a description of each test, the reader is referred to Lezak et al [2012]).

The novelty of our study is the demonstration that a multidomain, brief screening instrument can ascertain not only executive impairment in individuals with DM2, but also impaired social cognition. Social cognition impairment has been identified previously in individuals with DM1 (Kobayakawa, 2016; Kobayakawa et al, 2012; Zalonis et al, 2010) and was also confirmed in a recent meta-analysis of individuals with DM1 (Okkersen et al, 2017).

Verbal (Peric et al, 2015; Schneider-Gold et al, 2015) and nonverbal (Schneider-Gold et al, 2015; Weber et al, 2010) episodic memory impairment have been reported previously in individuals with DM2. In our study, 27% of the DM2 group showed impairment in verbal memory, yet by applying strict statistical criteria (P_{FDR} and BF > 10), the difference between the DM2 and HC groups was not significant.

In contrast to previous studies that reported visuospatial impairment (Peric et al, 2015, 2017b; Schneider-Gold et al, 2015), we did not detect significant visuospatial impairments; only 18% of our DM2 group scored in the abnormal range based on normative data. Inconsistencies between studies are important to outline future directions, define research strategies, and inform the design of future studies. In a recent review (Theodosiou et al, 2021), we showed that previous studies reporting impaired visuospatial functions used tests with high executive demands (Modoni et al, 2008), which tap into executive planning during complex figure copying (Shin et al, 2006); visuospatial tasks in the ECAS do not rely on executive functions. Language impairment has only been reported in individuals with DM2 with severe motor disability (Peric et al, 2017b), which is in line with the low percentage of patients (9% or 1/11) with abnormal language performance in our study.

Radiologic Findings

Our cognitive findings complement our radiologic observations. We found decreased GM density in the bilateral thalami and several frontal foci, including the bilateral fusiform gyri, left lingual gyrus, left middle occipital gyrus, left superior medial frontal gyrus, and bilateral calcarine gyri, as well as the right inferior frontal operculum, right precuneus, and right anterior cingulate. Our WM analyses did not capture statistically significant changes at $P < 0.05$ FWE.

There is considerable inconsistency in the literature regarding whether DM2 affects primarily WM or GM structures: Some studies have reported predominant WM changes

(Minnerop et al, 2008, 2011); others have identified widespread GM changes (Schneider-Gold et al, 2015). In our study, we detected multifocal cortical involvement, whereas the majority of previous studies reported global atrophy (Kassubek et al, 2003; Minnerop et al, 2011; Schneider-Gold et al, 2015; Weber et al, 2010).

Frontal changes have been consistently reported in the DM2 literature (Schneider-Gold et al, 2015; Weber et al, 2010), including PET and SPECT studies (Meola et al, 1999, 2003; Weber et al, 2010). Occipital involvement is less commonly detected by structural MRI studies (Schneider-Gold et al, 2015; Weber et al, 2010) but has been identified by a previous MR spectroscopy study (Vielhaber et al, 2006).

Existing multimodal studies have also explored the association between neuropsychological impairments and radiologic findings (Theodosiou et al, 2021). Cognitive flexibility was linked to the periaqueductal, midbrain, thalamus, parahippocampal gyrus, and anterior cingulate. The pattern of GM pathology we observed is highly consistent with the cognitive profile of our cohort. The observed executive impairments likely stem from the extensive frontal and thalamic pathology.

Social Cognition

One of the novel aspects of our study is the identification of impaired social cognition. In their pioneering study, Serra et al (2016) evaluated the underpinning of impaired social cognition in individuals with DM1 using resting-state fMRI analyses and identified a specific functional network that is responsible for physiological social cognition. This network entailed the frontal, temporal, occipital, and cerebellar areas. The same group recently reported a relationship between cortical thickness (occipital regions, precuneus, and medial frontal areas) and performance on social cognition tests in individuals with DM1 (Serra et al, 2020). Thus, we cannot exclude that the widespread occipital involvement that we observed

in our study may be linked to social cognition impairment. The occipital lobe has ample connectivity with anterior frontal and temporal regions through long association tracts.

Functional imaging studies using social cognition paradigms or neuropsychological tools and resting-state protocols have shown abnormal activation or co-modulation patterns in the occipital regions (Han et al, 2016; Taylor et al, 2011); highlighted the connectivity of the fusiform area to social cognition impairment; and supported that visual processing areas are functionally related to social cognition (Labbe et al, 2020), even in experimental paradigms in close to real-life conditions (Wolf et al, 2010). Structural neuroimaging studies have also identified significant correlations between decreased WM integrity in the left occipital WM region and facial emotional perception performance in individuals with schizophrenia (Miyata et al, 2010). The medial frontal regions, anterior cingulate, and precuneus have also been implicated in social cognition in other neurologic conditions (Christidi et al, 2018), including autism spectrum disorders (Patriquin et al, 2016).

Study Limitations

While this pilot study captured executive impairment in individuals with DM2, the sample size limitation of the study needs to be acknowledged. To overcome this shortcoming, we used strict statistical criteria not only by correcting for multiple comparisons (FDR), but also by reporting Cohen's |d| effect size and implementing the Bayes factor (BF_{10}). *P* values measure the difference between the data and the null hypothesis (H_0) (eg, the assumption of no difference or no effect), whereas the BF_{10} calibrates *P* values by converting them into evidence in favor of the alternative hypothesis (H_1) over the H_0 (Bland, 2015; Held and Ott, 2018). BF_{10} is considered substantially more parsimonious than the *P* value in evaluating evidence against the H_0 (Bland, 2015; Held and Ott, 2018). Also, the difference between BF_{10} and the *P* value in evaluating evidence against the H_0 is even greater in small sample sizes (Held and Ott, 2018).

Notwithstanding these observations, our group size is comparable with those of existing DM2 studies (Meola et al, 2003; Peric et al, 2017a), and individuals with DM2 have not previously been evaluated with a multidomain screening tool and neuroimaging. Future studies with larger sample sizes are warranted in order to replicate our findings. It is also important to use additional more specific and comprehensive neuropsychological tests of social cognition (eg, Reading the Mind in the Eyes task [Baron-Cohen et al, 2001], false-belief tasks [Bauminger-Zviely, 2013], Faux-Pas Test [Baron-Cohen et al, 1999; Gregory et al, 2002; Stone et al, 1998]). (For a comprehensive review of social cognition domains and assessment tools for clinical and research investigation and associated impairments in neurodegenerative conditions, please see Christidi et al [2018].) The multimodal longitudinal assessment of individuals with DM2 would also allow the characterization of propagation patterns radiologically and progressive neuropsychological changes, which so far have not been examined in Greek individuals with DM2 (Karatzikou et al, 2018; Papadimas et al, 2015; Papadopoulos et al, 2018).

Considering that cognitive impairment may be an integral feature of the DM2 phenotype, assessing cognition should always be considered in the clinical management of individuals with DM2. Executive impairment may affect patients' planning, reasoning, and/or problem-solving in everyday life conditions where they are required to manage multiple different tasks. The impact of different executive impairments needs to be studied specifically in association with impaired social cognition.

Impaired social cognition may negatively affect patients' interpersonal behavior and quality of life and progressively result in social isolation. On the other hand, memory impairment may affect patients' complex activities of daily living and interfere with their compliance with treatment approaches, including medication and nonpharmacological interventions.

Individuals with DM2 face a series of important decisions with regard to participation in clinical trials, research studies, employment, care preferences, and others. Therefore, we advocate for routine screening for cognitive impairment in individuals with DM2 using validated screening tests, which should be followed by formal neuropsychological evaluation by a trained neuropsychologist if severe impairment is suspected.

The identification of cognitive impairment in individuals with DM2 is also important for early interventions that may allow patients and their families to deal with cognitive impairments and reduce the negative impact of such impairments, including those related to social cognition (ie, reduced interpersonal network due to impaired emotional recognition and progressive social isolation). To the best of our knowledge, systematic cognitive rehabilitations programs with paper-and-pencil and/or computerized methods are lacking not only in individuals with DM2, but also in those with DM1.

CONCLUSION

Our pilot study suggests that DM2 may be associated with multifocal cortical and thalamic atrophy, which is likely to underpin the range of cognitive manifestations characterized mostly by executive impairment and specifically by impaired social cognition.

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REFERENCES

Abrahams S, Newton J, Niven E, et al. 2014. Screening for cognition and behaviour changes in ALS. *Amyotroph Lateral Scler Frontotemporal Degener.* 15:9–14. doi:10.3109/21678421.2013.805784

Bajrami A, Azman F, Yayla V, et al. 2017. MRI findings and cognitive functions in a small cohort of myotonic dystrophy type 1: retrospective analyses. *Neuroradiol J.* 30:23–27. doi:10.1177/1971400916678223

Baldanzi S, Cecchi P, Fabbri S, et al. 2016. Relationship between neuropsychological impairment and grey and white matter changes in adult-onset myotonic dystrophy type 1. *Neuroimage Clin.* 12:190–197. doi:10.1016/j.nicl.2016.06.011

Baron-Cohen S, O'Riordan M, Stone V, et al. 1999. A new test of social sensitivity: detection of faux pas in normal children and children with Asperger syndrome. *J Autism Dev Disord.* 29:407–418.

Baron-Cohen S, Wheelwright S, Hill J, et al. 2001. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry.* 42:241–251.

Bauminger-Zviely N. 2013. False-belief task. In: Volkmar FR, ed. *Encyclopedia of Autism Spectrum Disorders.* New York, New York: Springer. doi:10.1007/978-1-4419-1698-3_91

Bigler ED. 2017. Structural neuroimaging in neuropsychology: history and contemporary applications. *Neuropsychology.* 31:934–953. doi:10.1037/neu0000418

Bland M. 2015. *An Introduction to Medical Statistics*. 4th ed. Oxford, UK: Oxford University Press.

Cabada T, Iridoy M, Jericó I, et al. 2017. Brain involvement in myotonic dystrophy type 1: a morphometric and diffusion tensor imaging study with neuropsychological correlation. *Arch Clin Neuropsychol.* 32:401–412. doi:10.1093/arclin/acx008

Chen G, Carter RE, Cleary JD, et al. 2018. Altered levels of the splicing factor muscleblind modifies cerebral cortical function in mouse models of myotonic dystrophy. *Neurobiol Dis.* 112:35–48. doi:10.1016/j.nbd.2018.01.003

Christidi F, Migliaccio R, Santamaría-García H, et al. 2018. Social cognition dysfunctions in neurodegenerative diseases: neuroanatomical correlates and clinical implications. *Behav Neurol.* 2018:1849794. doi:10.1155/2018/1849794

Foley JA, Niven EH, Paget A, et al. 2018. Sensitivity and specificity of the ECAS in Parkinson's disease and progressive supranuclear palsy. *Parkinsons Dis.* 2018:2426012. doi:10.1155/2018/2426012

Gaul C, Schmidt T, Windisch G, et al. 2006. Subtle cognitive dysfunction in adult onset myotonic dystrophy type 1 (DM1) and type 2 (DM2). *Neurology.* 67:350–352. doi:10.1212/01.wnl.0000225180.27833.c1

Gourdon G, Meola G. 2017. Myotonic dystrophies: state of the art of new therapeutic developments for the CNS. *Front Cell Neurosci.* 11:101. doi:10.3389/fncel.2017.00101

Gregory C , Lough S, Stone VE, et al. 2002. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain*. 125:752–764. doi:10.1093/brain/awf079

Han M, Bi C, Ybarra O. 2016. Common and distinct neural mechanisms of the fundamental dimensions of social cognition. *Soc Neurosci.* 11:395–408. doi:10.1080/17470919.2015.1108931

Harley HG, Brook JD, Rundle SA, et al. 1992. Expansion of an unstable DNA region and phenotypic variation in myotonic dystrophy. *Nature.* 355:545–546. doi:10.1038/355545a0

Held L, Ott M. 2018. On *p*-values and Bayes factors. *Annu Rev Stat Appl.* 5:393–419. Doi:10.1146/annurev-statistics-031017-100307

Karatzikou M, Bakirtzis C, Nikolaidis J, et al. 2018. White matter hyperintensities in myotonic dystrophy type 2: not always another expression of the disease. *Mult Scler Relat Disord.* 24:117–119. doi:10.1016/j.msard.2018.06.020

Kassubek J, Juengling FD, Hoffmann S, et al. 2003. Quantification of brain atrophy in patients with myotonic dystrophy and proximal myotonic myopathy: a controlled 3-dimensional magnetic resonance imaging study. *Neurosci Lett.* 348:73–76. doi:10.1016/s0304-3940(03)00740-7

Kobayakawa M. 2016. Social cognitive impairment in myotonic dystrophy type 1. *Brain Nerve.* 68:137–144. doi:10.11477/mf.1416200363

Kobayakawa M, Tsuruya N, Kawamura M. 2012. Theory of mind impairment in adult-onset myotonic dystrophy type 1. *Neurosci Res.* 72:341–346. doi:10.1016/j.neures.2012.01.005

Kourtesis P, Christidi F, Margioti E, et al. 2020. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): sensitivity in differentiating between ALS and Alzheimer's disease in a Greek population. *Amyotroph Lateral Scler Frontotemporal Degener.* 21:78–85. doi:10.1080/21678421.2019.1655059

Labbe TP, Zurita M, Montalba C, et al. 2020. Social cognition in multiple sclerosis is associated to changes in brain connectivity: a resting-state fMRI study. *Mult Scler Relat Disord.* 45:102333. doi:10.1016/j.msard.2020.102333

Lee MD, Wagenmakers EJ. 2013. *Bayesian Cognitive Modeling: A Practical Course*. Cambridge, UK: Cambridge University Press.

Lezak MD, Howieson DB, Bigler ED, et al. 2012. *Neuropsychological Assessment.* 5th ed. New York, New York: Oxford University Press.

Meola G, Cardani R. 2015. Myotonic dystrophies: an update on clinical aspects, genetic, pathology, and molecular pathomechanisms. *Biochim Biophys Acta.* 1852:594–606. doi:10.1016/j.bbadis.2014.05.019

Meola G, Sansone V, Perani D, et al. 2003. Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myotonic myopathy (PROMM/DM-2). *Neuromuscul Disord.* 13:813–821. doi:10.1016/s0960-8966(03)00137-8

Meola G, Sansone V, Perani D, et al. 1999. Reduced cerebral blood flow and impaired visual–spatial function in proximal myotonic myopathy. *Neurology.* 53:1042–1050. doi:10.1212/wnl.53.5.1042

Michopoulos I, Douzenis A, Kalkavoura C, et al. 2008. Hospital Anxiety and Depression Scale (HADS): validation in a Greek general hospital sample. *Ann Gen Psychiatry.* 7:4. doi:10.1186/1744-859X-7-4

Minnerop M, Gliem C, Kornblum C. 2018. Current progress in CNS imaging of myotonic dystrophy. *Front Neurol.* 9:646. doi:10.3389/fneur.2018.00646

Minnerop M, Luders E, Specht K, et al. 2008. Grey and white matter loss along cerebral midline structures in myotonic dystrophy type 2. *J Neurol.* 255:1904–1909. doi:10.1007/s00415-008-0997-1

Minnerop M, Weber B, Schoene-Bake JC, et al. 2011. The brain in myotonic dystrophy 1 and 2: evidence for a predominant white matter disease. *Brain.* 134:3530–3546. doi:10.1093/brain/awr299

Miyata J, Yamada M, Namiki C, et al. 2010. Reduced white matter integrity as a neural correlate of social cognition deficits in schizophrenia. *Schizophr Res.* 119:232–239. doi:10.1016/j.schres.2009.12.038

Modoni A, Silvestri G, Vita MG, et al. 2008. Cognitive impairment in myotonic dystrophy type 1 (DM1): a longitudinal follow-up study. *J Neurol.* 255:1737–1742. doi:10.1007/s00415-008-0017-5

Mougias A, Christidi F, Kaldi M, et al. 2020. Mini-Mental State Examination: Greek normative data stratified by age and education in a large sample of 925 community-dwelling healthy participants. *Adv Exp Med Biol.* 1196:93–102. doi:10.1007/978-3-030-32637-1_9

Okkersen K, Buskes M, Groenewoud J, et al. 2017. The cognitive profile of myotonic dystrophy type 1: a systematic review and meta-analysis. *Cortex.* 95:143–155. doi:10.1016/j.cortex.2017.08.008

Papadimas GK, Kekou K, Papadopoulos C, et al. 2015. Phenotypic variability and molecular genetics in proximal myotonic myopathy. *Muscle Nerve.* 51:686–691. doi:10.1002/mus.24440

Papadopoulos C, Kekou K, Xirou S, et al. 2018. Early onset posterior subscapular cataract in a series of myotonic dystrophy type 2 patients. *Eye.* 32:622–625. doi:10.1038/eye.2017.280

Patriquin MA, DeRamus T, Libero LE, et al. 2016. Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder. *Hum Brain Mapp.* 37:3957–3978. doi:10.1002/hbm.23288

Peric S, Brajkovic L, Belanovic B, et al. 2017a. Brain positron emission tomography in patients with myotonic dystrophy type 1 and type 2. *J Neurol Sci.* 378:187–192. doi:10.1016/j.jns.2017.05.013

Peric S, Mandic-Stojmenovic G, Stefanova E, et al. 2015. Frontostriatal dysexecutive syndrome: a core cognitive feature of myotonic dystrophy type 2. *J Neurol.* 262:142–148. doi:10.1007/s00415-014-7545-y

Peric S, Rakocevic Stojanovic V, Mandic Stojmenovic G, et al. 2017b. Clusters of cognitive impairment among different phenotypes of myotonic dystrophy type 1 and type 2. *Neurol Sci.* 38:415–423. doi:10.1007/s10072-016-2778-4

Radovanović S, Perić S, Savić-Pavićević D, et al. 2016. Comparison of temporal and stride characteristics in myotonic dystrophies type 1 and 2 during dual-task walking. *Gait Posture.* 44:194–199. doi:10.1016/j.gaitpost.2015.12.020

Romeo V, Pegoraro E, Ferrati C, et al. 2010. Brain involvement in myotonic dystrophies: neuroimaging and neuropsychological comparative study in DM1 and DM2. *J Neurol.* 257:1246–1255. doi:10.1007/s00415-010-5498-3

Schneider-Gold C, Bellenberg B, Prehn C, et al. 2015. Cortical and subcortical grey and white matter atrophy in myotonic dystrophies type 1 and 2 is associated with cognitive impairment, depression and daytime sleepiness. *PloS One.* 10:e0130352. doi:10.1371/journal.pone.0130352

Serra L, Bianchi G, Bruschini M, et al. 2020. Abnormal cortical thickness is associated with deficits in social cognition in patients with myotonic dystrophy type 1. *Front Neurol.* 11:113. doi:10.3389/fneur.2020.00113

Serra L, Cercignani M, Bruschini M, et al. 2016. "I know that you know that I know": neural substrates associated with social cognition deficits in DM1 patients. *PloS One.* 11:e0156901. doi:10.1371/journal.pone.0156901

Shin MS, Park SY, Park SR, et al. 2006. Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. *Nat Protoc.* 1:892–899. doi:10.1038/nprot.2006.115

Stone VE, Baron-Cohen S, Knight RT. 1998. Frontal lobe contributions to theory of mind. *J Cogn Neurosci.* 10:640–656. doi:10.1162/089892998562942

Taylor SF, Chen AC, Tso IF, et al. 2011. Social appraisal in chronic psychosis: role of medial frontal and occipital networks. *J Psychiatr Res.* 45:526–538. doi:10.1016/j.jpsychires.2010.08.004

Theodosiou T, Christidi F, Xirou S, et al. 2018. Identifying neuropsychological dysfunctions of Myotonic Dystrophy Type 2 in everyday clinical practice. Oral talk presented at: 1st Panhellenic Congress on Neuropsychology; April 27–29, 2018; Athens, Greece.

Theodosiou T, Christidi F, Xirou S, et al. 2021. Neuropsychological assessment should always be considered in myotonic dystrophy type 2. *Cogn Behav Neurol.* 34:1–10. doi:10.1097/WNN.0000000000000263

Udd B, Krahe R. 2012. The myotonic dystrophies: molecular, clinical, and therapeutic challenges. *Lancet Neurol.* 11:891–905. doi:10.1016/S1474-4422(12)70204-1

Vielhaber S, Jakubiczka S, Gaul C, et al. 2006. Brain 1H magnetic resonance spectroscopic differences in myotonic dystrophy type 2 and type 1. *Muscle Nerve.* 34:145–152. doi:10.1002/mus.20565

Weber YG, Roebling R, Kassubek J, et al. 2010. Comparative analysis of brain structure, metabolism, and cognition in myotonic dystrophy 1 and 2. *Neurology.* 74:1108–1117.

Wolf I, Dziobek I, Heekeren HR. 2010. Neural correlates of social cognition in naturalistic settings: a model-free analysis approach. *Neuroimage.* 49:894–904. doi:10.1016/j.neuroimage.2009.08.060

Yum K, Wang ET, Kalsotra A. 2017. Myotonic dystrophy: disease repeat range, penetrance, age of onset, and relationship between repeat size and phenotypes. *Curr Opin Genet Dev.* 44:30–37. doi:10.1016/j.gde.2017.01.007

Zalonis I, Bonakis A, Christidi F, et al. 2010. Toward understanding cognitive impairment in patients with myotonic dystrophy type 1. *Arch Clin Neuropsychol.* 25:303–313. doi:10.1093/arclin/acq016