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Neurobiological bases of Theory of Mind in Myotonic dystrophy Type-1

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy observed in adults[1]. It is caused by a CTG triplet repeat expansion within the myotonic dystrophy protein kinase (DMPK) gene located on chromosome 19q13.3, whose inheritance is autosomal dominant[1] . DM1 is a multi-systemic disorder dominated by muscular impairment, but involving also other organs including the brain[1]. Previous literature showed that most of the cognitive impairment observed in patients with non-congenital DM1 is driven by higher-level dysfunctions[2-3]. Structural[3-4]and functional changes[2] were previously demonstrated in DM1 brains, and these changes have been found to be associated with isolated cognitive deficits[3-4] and with personality disorders[2]. However, a paradoxical mismatch exists between the widespread brain damage observed in DM1, their relative preservation of global cognition and their failure in everyday life. One possible explanation is that in non-congenital forms of DM1 this difficulty in daily living is due to a dysfunction of social cognition, rather than more basic cognitive abilities. Recently, Kobayakawa and co-workers[5] found that patients with DM1 fail in tests assessing the theory of mind (ToM), an important component of social cognition functioning. ToM refers to the ability to infer other people's mental states, thoughts and feelings. ToM is necessary to empathize and have a good relationship with others in social situations[6]. Previous task-related functional MRI (fMRI) studies demonstrated that ToM abilities depended on the integrity of several brain regions, mainly the medial prefrontal cortex, the cingulum, the precuneus, the temporal, and occipital regions[7]. It has also been shown that the identification of the neural basis underling the ToM is material-dependent[7]. Indeed, several tests can be used to assess ToM, some of them are story-based, which can be presented either verbally or visually, others are administered using non-story-based visual stimuli, such as the "Reading the Mind in the Eyes" test[8]. Against this background, it is conceivable that one or more networks, rather than isolated regions, subserve ToM, and that abnormal connectivity within these networks might explain ToM deficits in DM1. Resting-state functional MRI (RS-fMRI)[9] is one of the most widely used methods to investigate brain connectivity in neurological and psychiatric diseases, with the advantage of not requiring participants to perform any active task. RS-fMRI data can be analysed using different methodological approaches. A recently introduced technique is based on the whole-brain analysis driven by graph theory[10], a mathematical approach that describes complex systems as networks[10]. In simple words, the brain is represented by a number of regions (nodes) that are functionally connected to each other by edges. The edges can be computed from RS fMRI data. In this view, nodes with many connections are more critical (i.e., more "central") for transferring information across the network, and are called "hubs". Abnormal connectivity between "hubs" is believed to cause more relevant deficits than that between peripheral nodes[10] . To the best of our knowledge, no previous attempt was made to identify a "ToM" network using graph-theory approaches, or to assess the related functional connectivity changes in DM1. The present work was thus designed 1) to identify the so-called ToM-network, in patients with DM1, and 2) to investigate the differences in the topological properties of the ToM-network between DM1 patients and healthy controls.

METHODS

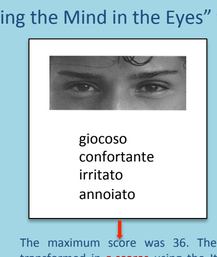
20 DM1 patients

Mean (SD) age [years]: 43.9 (10.7)
Gender (F/M): 11.0/9.0
Mean (SD) years of formal education: 13.0 (2.6)
MMSE>26
CTG triples range: 54-2000
% MIRS stages:
Stage 2: 30.0%
Stage 3: 55.5%
Stage 4: 15.0%

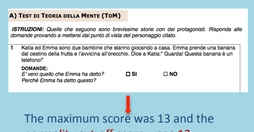
18 HS were used for functional brain connectivity analysis
Mean (SD) age [years]:42.7 (12.4)
Gender (F/M): 10.0 /8.0
Mean (SD) years of formal education: 15.0 (3.2)

ToM evaluation

Reading the Mind in the Eyes" test (RMET)[8] + Theory of Mind stories[11]



The maximum score was 36. The hit-rates were transformed in z-scores using the Italian Normative data as a reference[8].
Z-score≤0 = pathological performance.
Moreover we computed also the number of errors in the males' (EM) and females' (EF) pictures separately

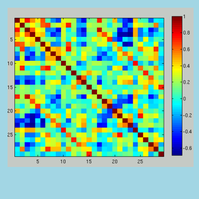


The maximum score was 13 and the normality cut-off score was ≥12 accordingly to the Italian Normative data[11]

To obtain a single comprehensive score of ToM (named ToM Composite score ToMCs) to correlate with MRI data, Principal Component Analysis (PCA) was applied to the three available scores (RMET-hit rates, RMET-EM, ToM-story) to assess the theory of mind abilities.

RS-fMRI

1) Each image was pre-processed to obtain the connectivity matrix

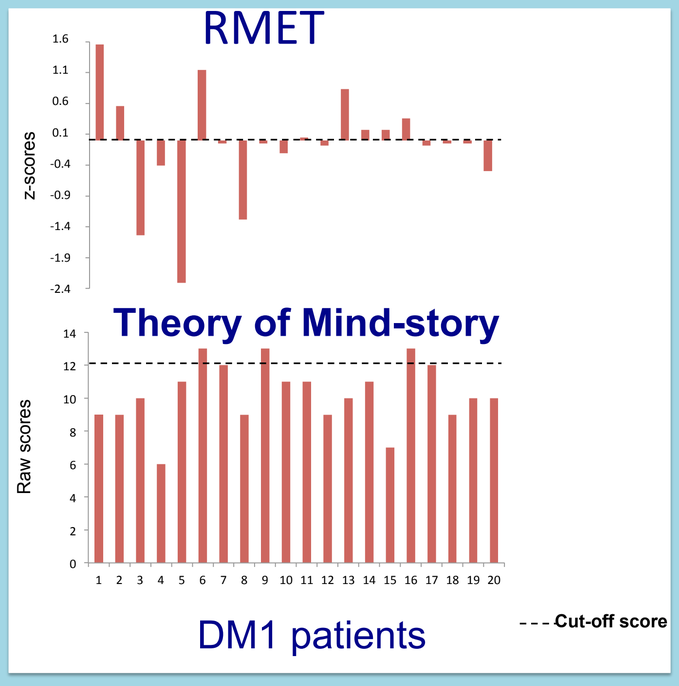


2) The Network-based statistics (NBS) approach was used to identify a ToM network in DM1 patients correlating each connectivity matrix with the patient's ToMCs . Correlation with ToMCs was based on one-sample t-test, using 5000 permutations and setting the significant p-value at 0.05 [corrected for multiple comparisons].

3) The Graph theory was used to investigate the topological properties of the ToM-network in patients and controls. We focussed on a subset of global properties, primarily assessing segregation and integration. With respect to local metrics, we considered betweenness centrality, nodal degree, and nodal efficiency. Betweenness centrality is defined as the fraction of all the shortest paths passing through a given node; nodal degree expresses the number of connections for each node; nodal efficiency is inversely related to each node's paths length, and identifies the less efficient nodes along certain routes. For each considered global and local measure of connectivity, a two-sample t-test was used to assess group differences between DM1 patients and controls.

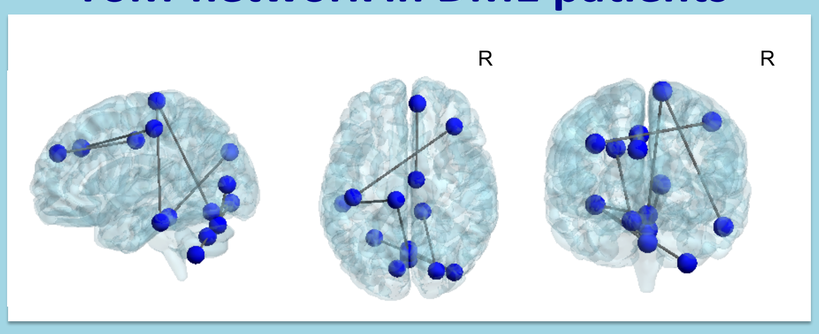
RESULTS

ToM evaluation



Patients with DM1 reported performances below the normality cut-off score in both tests assessing the ToM abilities. In particular, 12 patients (60%) underperformed at the RMET (Figure 1, panel A) and 15 patients (75%) reported low scores at ToM-story task (Figure 1, panel B).
We found a negative correlation between patients' RMET hit-rates scores and their CTG triplets' expansion (r=-0.49, p=0.04). No other correlations were found.

ToM-network in DM1 patients



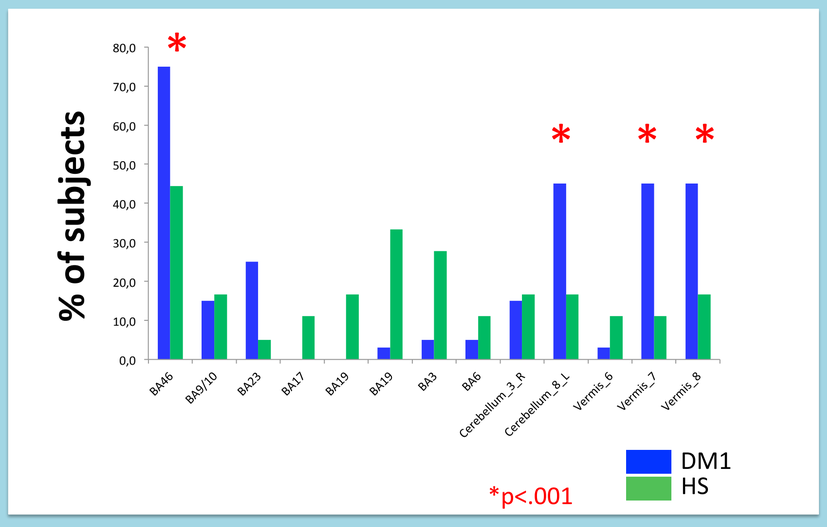
Significant positive correlation between brain networks connecivity and ToMCs in patients with DM1.

The brain network significantly associated with ToMCs involved 14 nodes and 9 edges. This network encompassed frontal (BAs: 6, 9/10; 23; 46), temporal (BA: 20), occipital (BAs: 17; 19) and cerebellar (Lobules 3, 8 and Vermis) areas.

When comparing the topological properties of the ToM-network between DM1 patients and HS, graph analysis revealed no differences in measures of global connectivity. Conversely, centrality measures (nodal efficiency and degree) were found significantly increased in a node located into the BA20 in DM1 patients compared to HS.

Based on these results, we performed further analyses on the specific connections between BA20 and the remaining 13 nodes of the ToM - network. Specifically, for each of these connections we computed the frequency of occurrence (i.e., in how many subjects per group that connection was present), and we compared it between DM1 patients and healthy controls using Chi-square statistics.

Frequency of occurrence of direct connections between BA20 and the rest of ToM network.



BA20 resulted connected with BA46 in 75.0% of DM1 patients (15 out of 20) and in 44.4% (8 out of 18) of healthy controls (Chi-square=19.9 d.f.=1, p<0.001); BA20 was connected with the cerebellum (lobule 8 and vermis 8) in 45.0% (9 out of 20) of DM1 patients and in 16.6% (3 out of 18) of healthy controls (Chi-square=19.8 d.f.=1, p<0.001), and finally, BA20 was connected with cerebellum (with vermis 6 and with vermis 7) in 45.0% (9 out of 20) of DM1 patients and in 11.1% (2 out of 18) of healthy controls.
Conversely, connections between BA20 and occipital regions were observed only in the control group.

DISCUSSION

This study confirms that ToM deficits exist in DM1 patients. Additionally, it reveals that those deficits are likely associated with a maladaptive increase of functional brain connectivity in areas traditionally involved in social cognition abilities. We argue that these abnormalities impact not only on behavioral symptoms, but also on mentalizing abilities, as observed in also psychiatric disorders.

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