Ventral tegmental area dysfunction affects decision-making in patients with myotonic dystrophy type-1

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Author Contribution

MBo conceived and supervised the study in all its parts (patient recruitment, MR scanning, neuropsychological assessments, data analysis and interpretation) and wrote the manuscript.

LS contributed to conceive the study, did MR scanning, supervised neuropsychological testing, analysed the data, contributed to writing up the manuscript.

MS, MBr, CDD contributed to patient neuropsychological assessment and MR scanning.

GM, MDA, GK, LP, and CC contributed to data interpretation and discussion.

MC set up the MR protocol, supervised image analysis, contributed to write up the methodological sections of the manuscript.

GS and AP did patient recruitment and clinical assessment, and contributed to data interpretation and discussion.

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Abstract

The clinical manifestations of Myotonic Dystrophy type-1 (DM1) are associated with a complex mixture of multisystem features including cognitive dysfunctions that strongly impact on patients' social and occupational functioning. Decision making, a function controlled by dopaminergic circuitry, is critical for succeeding in one's social and professional life. We tested here the hypothesis that altered connectivity of the ventral tegmental area (VTA), one of the major sources of diffuse dopaminergic projections in the brain, might account for some higher-level dysfunctions observed in patients with DM1. In this case-control study, we recruited 31 patients with DM1 and 26 healthy controls who underwent the IOWA Gambling task and resting-state functional MRI (RS-fMRI) at 3T. Functional connectivity of the VTA was assessed using RS-fMRI. VTA connectivity was compared between 25 DM1 patients and all the controls, and the presence of associations between VTA connectivity and IOWA Gambling task performance was also investigated. DM1 patients performed significantly worse than controls at the IOWA Gambling task. A significant increase of functional connectivity was observed between VTA and the left supramarginal and superior temporal gyri in DM1 patients. Patients' IOWA Gambling task net-scores were strictly associated with VTA-driven functional connectivity in the bilateral supplementary motor area and right precentral gyrus. This study demonstrates a prominent deficit of decision-making in patients with DM1. It might be related to increased connectivity between VTA and brain areas critically involved in the reward/punishment system and social cognition. These findings indicate that dopaminergic function is a potential target for pharmacological and non-pharmacological interventions in DM1.

Key-words: DM1; dopamine; fMRI; connectivity; cognition.

1. Introduction

Myotonic dystrophy type-1 (DM1) is an autosomal dominant muscular dystrophy caused by a pathological CTG triplet repeat expansion in the myotonic dystrophy protein kinase (DMPK) gene located on chromosome 19q13 (Meola & Cardani, 2015). DM1 is a composite clinical condition affecting not only the skeletal muscles but also various organs including the brain. The neuropsychiatric manifestations of DM1 are a complex mixture of personality disorders and higher-level cognitive dysfunctions that strongly impact on patients' social functioning (Serra et al., 2014; Serra et al., 2015; Serra et al., 2016a). When tested on single cognitive domains, such as memory, attention, language and visuo-spatial activities, DM1 patients typically perform better than expected (Gaul et al., 2006). In contrast, they perform poorly when assessed for high-order executive functions such as social cognition (Serra et al., 2016a). We have previously shown that failure in the daily life of DM1 patients is at least partially explained by theory of mind deficits, which are associated with peculiar changes of functional brain connectivity (Serra et al., 2016a). Nonetheless, other cognitive abilities are known to be implicated in the complex process of interaction with the environment, which adapt and modify human behaviours according to environmental modifications. "Decision-making" is defined as the ability to take decisions among different alternatives on the basis of an obtainable profit (Bechara, Damasio, Damasio & Anderson, 1994) The reward / punishment system is directly involved in decision-making. Several measures can be used to assess the decision-making abilities, the Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio & Anderson, 1994) being the most popular. IGT was developed to simulate real-life decisions and assess different patterns of decision-making between healthy subjects and patients with ventromedial prefrontal lesions and deficits in social functioning (Bechara, Damasio, Damasio & Anderson,

1994; Lin, Song, Lin & Chiu YC, 2012). Using IGT, decision-making dysfunctions have also been extensively demonstrated in several psychiatric (e.g., pathological gamblers; patients with schizophrenia) (Ciccarelli, Griffiths, Nigro & Cosenza, 2017; Saperia et al., 2019) and neurological disorders (i.e., patients with Parkinson's disease and other neurodegenerative disorders; patients with traumatic brain injuries) (Gleichgerrcht, Ibáñez, Roca, Torralva & Manes, 2010; Zamarian, Weiss & Delazer M, 2010; Yasuno et al., 2014).

A widespread fronto-striatal cortical-subcortical circuitry is involved in the decision-making abilities and in the reward system (van Holst, van den Brink, Veltman, & Goudriaan, 2010). In fact, orbito-prefrontal and ventromedial prefrontal cortices together with their subcortical projections are strictly involved in these functions (van Holst, van den Brink, Veltman, & Goudriaan, 2010). It is well known that dopamine plays a prominent role in the decision-making abilities as well as in behavioural functions (Schaeffer & Berg et al., 2017; Chong & Husain, 2016; Kessler, Hutson, Herman & Potenza, 2016; Serra et al., 2018). Nevertheless, the precise cellular and molecular mechanisms underlying the clinical symptoms and alterations in brain connectivity are still far from being fully understood. Interestingly, a recent study based on a transgenic mouse model of DM1 highlighted a potential pathophysiological role for the dopamine (DA) circuitry in determining DM1 mice behavioural features (Ramon-Duaso et al., 2018). Significant alterations in the DA transport system, DA receptors, and DA levels were identified in the medial prefrontal cortex of the DM1 animal model (Ramon-Duaso et al., 2018).

In the DM1 animal model, the anatomical distribution of dopaminergic dysfunction was mainly observed in the prefrontal cortex (Ramon-Duaso et al., 2018). In humans, the prefrontal cortex is strongly implicated in higher-level cognitive and

behavioural functions as part of a more widespread network that is mainly modulated by subcortical dopaminergic projections (Ranganath & Jacob, 2016). Among these, there is the ventral tegmental area (VTA), a brainstem structure, which is particularly rich in dopaminergic neurons that project diffusely to several subcortical and cortical areas, including the prefrontal cortex (Schultz, Dayan & Montague, 1997). This complex system is mainly implicated in reward mechanisms as shown in previous animal (Schultz, Dayan & Montague, 1997) and human studies (Krebs, Heipertz, Schuetze & Duzel, 2011; Richter & Gruber, 2018).

Against this background, we hypothesise that some dopaminergic dysfunction might occur and play a significant role in determining some of the higher-level dysfunctions observed in DM1 patients. In particular, based on the results in the animal model (Ramon-Duaso et al., 2018) and on previous evidence of increased functional connectivity in DM1 patients, we anticipate that patients with DM1 might show increased connectivity within networks related to reward-based decision-making processes, which are induced by hyper-functioning VTA dopaminergic neurons.

Resting-state functional MRI (fMRI) is a robust approach to investigate brain connectivity *in vivo*, which has recently been successfully used to investigate VTA-driven changes in brain connectivity in humans (Serra et al., 2018). To test the hypothesis that VTA-driven connectivity might contribute to DM1 decision-making dysfunctions, we recruited a group of patients with DM1 and a group of healthy controls in a case-control design. They were tested with the IGT, and underwent a resting-state fMRI session. In DM1 patients we predicted an increased pattern of VTA-driven connectivity in association with a decreased performance on IGT.

2. Materials and Methods

2.1.Study design and power calculation

This is a case-control study, with two groups: patients with DM1 and healthy controls. The main outcome measure is the performance at the IGT. As this is an exploratory study, there is no data available to compute the effect size. However, previous studies based on this test have shown typically large effect sizes (Bechara, Damasio, Damasio, Anderson, 1994; Bechara & Damasio, 2002). Therefore, a statistical power analysis was performed for sample size estimation for ANOVA (F test), with an alpha=.05 and power=0.80. The projected sample size needed with an effect size of 0.4 (GPower 3.1) was approximately N = 50 in total. No part of the study procedures and analyses was pre-registered prior to the research being conducted.

2.2. Participants

Thirty-one patients with a molecular diagnosis of DM1 were recruited from the Neuromuscular and Neurological Rare Diseases Centre at San Camillo Forlanini Hospital (Rome, Italy) and from the Institute of Neurology at the Catholic University of Rome (Rome, Italy) between March 2016 and December 2018. Molecular diagnosis was performed as described previously (IDMC, 2004). Patients were selected to have either an adulthood (62.5%) or a childhood-juvenile (40.1%) disease onset [mean (SD) CTG triplets expansion: 467 (272); mean (SD) Muscular Impairment Rating Scale (MIRS) (Mathieu, Boivin, Meunier, Gaudreault & Bégin, 2001) score: 2.8 (0.7)], whereas patients with a congenital disease onset were excluded. Twenty-six healthy subjects (HS), age and gender matched to the patients, were recruited through classified advertisements and through the dedicated mailing lists of Fondazione Santa Lucia (Rome, Italy), and served as controls for this study. The principal demographic and clinical characteristics of all participants are summarized in Table 1. All participants

were right handed as assessed by the Edinburgh Handedness Inventory (Büsch, Hagemann & Bender, 2010). A clinical assessment was run to exclude the presence of any pathologies different from known comorbidities in DM1 patients and major systemic or neurological illness in the control group. The study was approved by the Ethical Committee of Santa Lucia Foundation and written informed consent was obtained from all participants before study initiation. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.3.Neuropsychological assessment

As part of the screening process, all DM1 patients were first evaluated using the social cognition battery (Prior, Marchi & Sartori, 2003) and the Coloured Progressive Raven's Matrices (Carlesimo, Caltagirone & Gainotti, 1996). For the purpose of the current study, they also underwent the IGT (Bechara & Damasio, 2002) to assess risk preferences by simulating real-life decision-making ~~and~~ using uncertain rewards and penalties. One-hundred cards from 4 virtual decks (A, B, C, D) were presented on a computer screen, and participants were instructed to choose a card from one deck. They were told that every card would either win or lose them some game money. The goal of the game was to win as much money as possible. All decks contained both winning and losing cards, but Decks A and B were set to be disadvantageous (leading to an overall loss), while decks C and D were set to be advantageous (leading to an overall gain). Participants ignored how many cards had to be turned before the game ended. At the end of the game, the overall total net score [i.e., (C+D)-(A+B)] was calculated.

Highly positive net scores indicate that advantageous decks were preferentially chosen in comparison to those that were disadvantageous, thus reflecting a preferential attitude in taking low-risk choices. Conversely, low net scores reflect the absence of a

preferential choice between decks, thus showing an inability to perform the necessary risk evaluation to get a potential reward. Finally, negative net scores indicate the preference to select high-risk decks (i.e. disadvantageous decks).

Statistical analyses were performed using SPSS-21 (SPSS Inc., Chicago, Illinois). The performance at IGT was the primary outcome measure of the study and was assessed by means of deck choice using a two-way ANCOVA [Group (DM1 *vs.* HS) X Trial (Deck A *vs.* Deck B *vs.* Deck C *vs.* Deck D)], and by means of overall score by using a one-way ANOVA (Group X Net-score). Both analyses were adjusted for age and years of formal education.

2.4.Image acquisition and pre-processing of resting-state fMRI

All participants underwent an MRI scan at 3T including the following acquisitions: 1) T2* weighted echo planar imaging (EPI) sensitized to blood oxygenation level dependent (BOLD) contrast (TR=2080 ms, TE=30 ms, 32 axial slices parallel to AC-PC line, matrix=64x64, pixel size=3x3 mm2, slice thickness=2.5 mm, flip angle:70°) for resting-state fMRI; 2) a 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix=256x224, n. slices=176, thickness=1 mm) to be used as anatomical reference. BOLD EPIs were collected during rest for 7 min and 20 s, resulting in a total of 220 volumes. During the acquisition, participants were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. Images were pre-processed for resting-state fMRI using Statistical Parametric Mapping version 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm/), and in-house Matlab scripts as previously described (Serra et al., 2018; Bozzali et al., 2015). Briefly, every participant's MDEFT was segmented in SPM8 in order to obtain probabilistic images of CSF, grey and white matter. The grey matter images were used to estimate the participant-specific total GM

volume (which was used to adjust the functional connectivity analysis). White matter and CSF images were thresholded to compute participant-specific masks of either tissue. The mean fMRI signal for both white matter and CSF was extracted using these masks.

In order to assess the functional connectivity between VTA and the rest of the brain we followed a pipeline specifically developed for this purpose and previously described (Serra et al., 2018). For each participant, the first four volumes of the fMRI series were discarded to allow for T1 equilibration effects. The pre-processing steps included correction for head motion, compensation for slice-dependent time shifts, and normalization to the EPI template in MNI coordinates provided with SPM8. For each data set, motion correction was checked to ensure that the maximum absolute shift did not exceed 1.5 mm and the maximum absolute rotation did not exceed 1°. Datasets not fulfilling these criteria were excluded from further analyses (i.e., 6 patients and 8 healthy subjects). The signal in every voxel was regressed against the average white matter and CSF signals (computed as explained above), as well as against the 6 realignment parameters. Then, all images were filtered by a phase-insensitive band-pass filter (pass band 0.01–0.08 Hz) to reduce the effect of low-frequency drift and high-frequency physiological noise. We refer to these datasets as unsmoothed corrected data. These data were then smoothed via filtering with a 3D Gaussian kernel with 10 mm^3 full width at half maximum.

2.5. Seed-Based Analyses

As previously described (Serra et al., 2018), standard space seed masks of the left and right VTA were produced by using the Harvard Ascending Arousal Network Atlas in MGH152_1mm Space (https://www.martinos.org/) (Edlow et al., 2012) (Figure 1). A single seed mask was obtained combining left and right regions.

Insert Figure 1 around here

The mean time course within each seed region was extracted (from the unsmoothed corrected data) for every participant. The unsmoothed data were chosen for this step in order to minimize the partial volume contamination from neighbouring nuclei. The smoothed data were then regressed voxel-wise against these time courses in a first-level SPM8 analysis. The resulting beta images were taken to the second level for a random-effect group analysis. Finally, at second level, a t-test model was used to assess between-group differences (25 DM1 patients *vs.* 18 HS) in VTA functional connectivity. Age and education were used as covariate of no interest.

Next, we assessed the potential associations between the IGT net-score and functional connectivity changes in DM1 patients and HS using a one-sample t-test model. Statistical significance was always set at $p < 0.05$ FWE-corrected at cluster level (clusters formed with $p<0.001$ at voxel level).

2.6.Data availability statement

The datasets analyzed during the current study are available from the Corresponding Author on request.

3. Results

3.1.Demographic, clinical and neuropsychological characteristics

Patients and controls were not significantly different in age or gender distribution ($F_{1,55}=0.02$, p=0.864; Chi-square=0.08, p=0.78). As expected, there was a significant difference between patients and controls in the years of formal education ($F_{1,55}=59.8$, p=0.000) (Table 1). Patients showed normal visuo-spatial logical reasoning abilities (mean $\pm$ SD Raven score: 28.1$\pm$6.8; cut-off $\geq$ 18.9). Conversely, when using the social cognition screening battery, 25 out of 31 patients (80.6%) performed below

the normality cut-off score on the Story Test (mean ± SD score 9.4±2.8; cut-off ≥ 12). All these findings replicate and extend previous data (Serra et al., 2016a), thus delineating a peculiar neuropsychological profile in DM1 patients.

3.2.Decision-making performance

When considering the decks' choice (Figure 2A) there was a significant Group effect ($F_{1,55}$=5.41, p=0.023) due to the poor performance of DM1 patients. There was also a significant Trial effect ($F_{1,168}$=18.3, p<0.001) due to the more frequent selection of Deck B (mean of chosen cards=30.0), followed by Deck D (mean of chosen cards=28.5), Deck C (mean of chosen cards=22.7) and Deck A (mean of chosen cards=18.9). There was no significant Group by Trial interaction (F1,168=1.7, p=0.15). Both groups preferentially selected the disadvantageous Deck B. This is a well-known effect (i.e., the prominent Deck B phenomenon) that has been previously described in healthy (Lin, Song, Lin & Chiu YC, 2012; Fernie & Tunney, 2006) as well as in pathological populations (Ritter, Meador-Woordruff & Dalack, 2004). All individuals are indeed insensitive to the long-term outcomes and they demonstrate a short-sightedness in situations that involve uncertainty. However, HS, but not DM1 patients, compensated the choice of disadvantageous Deck B by selecting more cards from the advantageous Decks C and D. When considering the net-score (Figure 2B), a significant Group effect (F3,54=4.28; p=0.009) was found, due to the negative net-scores of DM1 patients (mean net-score= -1.44) that was significantly different from the positive net-score of HS (mean net-score=15.6). The patients' negative net-score suggests a pathological behaviour (i.e., propensity to an immediate high gain regardless of delayed high losses) going beyond an attitude to take high-risk choices.

Insert Figure 2 around here

3.3. Resting-state fMRI

Images from six DM1 patients showed the presence of movement artefacts and were for this reason excluded from the image analyses. The RS-fMRI analyses were therefore run on 25 DM1 patients and 26 HS.

DM1 patients compared to HS revealed a significant increase of functional connectivity between VTA and the left supramarginal gyrus (BA40) and the left superior temporal gyrus (BA41) (Figure 3).

Insert Figure 3 around here

In DM1 patients, there were negative correlations between IGT's net-scores and VTA-driven functional connectivity in the bilateral supplementary motor area (BA6) (Figure 4) and in the right precentral gyrus (BA4). No significant correlations were found in the HS group.

Insert Figure 4 around here

4. Discussion

The present study shows for the first time the presence of decision-making deficits in patients with DM1, and their association with abnormal patterns of VTA-driven brain connectivity. Brain connectivity was found here to be abnormally increased in DM1 patients, specifically between the VTA and brain areas, which are devoted to higher-level functions. Increased connectivity within areas of the association cortex has been consistently reported in the literature (Serra et al., 2014; Serra et al., 2016a; Minnerop et al, 2011; Serra et al., 2016b), and perhaps might represent a peculiar trait of this complex disorder. Previously, in DM1, increased patterns of connectivity were found in critical areas of the default-mode network (Serra et., al 2014) and in the fusiform gyrus (Minnerop et al, 2011), which were associated with or contributed to

explain patients' personality traits (Serra et., al 2014). Similarly, increased patterns of network connectivity were identified in association with the severity of patients' deficits in social cognition (i.e., Theory of Mind) (Serra et al., 2016a). All these data support the hypothesis that increased brain connectivity may represent the neurobiological substrate for the cognitive and behavioural manifestations observed in DM1. As anticipated in the introduction section, the exact meaning of increased connectivity remains unclear.

Indeed, it should be noted that previous fluorodeoxyglucose (FDG)-positron emission tomography (PET) have reported patterns of decreased metabolism in DM1 brains, particularly in frontotemporal areas (Weber et al., 2010; Renard et al., 2016; Peric et al., 2017). This is in apparent contrast with our hypothesis. However, the relationship between brain metabolism and fMRI connectivity remains largely unclear (Savio et al., 2017). Further clarifications might stem from studies using DAT-SPECT or Dopa/reclopride-PET in DM1 patients, investigating the relationship between neurotransmission, metabolism, and connectivity. It should also be noted that functional connectivity measures the correlation between brain activity in segregated brain areas (at rest), and not the activity itself. Therefore, it does not necessarily imply increased or decreased metabolism. The combination of increased brain connectivity with microstructural brain tissue abnormalities (Serra et al., 2015; Minnerop et al., 2011; Gliem et al., 2019), that are strictly associated with patients' genetic loads (Serra et al., 2015), suggests that, in DM1, complex neurodevelopmental modifications may result in complex higher-level dysfunction. Critically, the current study reveals abnormal connectivity between VTA and temporo-parietal brain regions. As VTA is rich in dopaminergic neurons, it is reasonable to speculate that such abnormalities might be driven, at least partially, by a selective subcortical involvement of the dopaminergic system. Notably the present findings are consistent with those reported in a recent study

based on an animal model of DM1 (i.e., Mbnl2 knockout mouse) (Ramon-Duaso et al., 2018). Ramon-Duaso and Co-authors reported, in Mbnl2 knockout mice, the occurrence of progressive cognitive and affective alterations associated with hyperactivation of the dopaminergic system within the prefrontal cortex (Ramon-Duaso et al., 2018). Moreover, such a dopaminergic modulation was associated with profound perturbations in neural activity and microgliosis, thus suggesting a relationship between dopaminergic modulation and microstructural brain tissue modifications. Of course, without evidence of dopaminergic dysfunction in our sample, we can only speculate that our findings might reflect a similar mechanism. Further studies are needed to clarify the pathology underpinning our findings, and therefore their potential relevance for future developments in the pharmacological treatment of DM1, not only in a symptomatic perspective, but also in terms of potential disease-modifying therapies.

Nevertheless, it remains to be clarified whether increased functional connectivity may be regarded as a measure of hyperfunctioning dopaminergic neurons or may rather reflect some compensatory mechanisms consequent to hypofunctioning of the dopaminergic system. Future in vivo studies using dopaminergic tracers are mandatory to address this issue.

All DM1 patients recruited here had an adult or childhood-juvenile disease onset, and showed a severe impairment of social cognition with sparing of logical abilities. When tested using the IGT, DM1 patients showed a substantial impairment in their decision-making abilities. Critically, their negative net score on the IGT indicates a pathological behaviour in taking high-risk decisions aimed to achieve an immediate reward and an instantaneous gratification. This behaviour is an expression of patients' impulsivity and inability to inhibit maladaptive conducts. In real life, this dysfunction in decision-making abilities might account for DM1 patients' difficulties in social and

professional interactions, and probably shares some common aspects with their personality traits (Serra et al., 2014).

In terms of neuronal substrate, decision-making is a complex process that involves both cortical and subcortical circuits. While the subcortical dopaminergic areas respond to reinforced stimuli and induce a prompt reaction for an immediate reward, the cortical areas inhibit the instinctual behaviours to obtain more functional long-term gains through the activation of the cognitive and impulse control systems. Subcortical and cortical abnormalities within this neuronal circuitry have been described in other neurological and psychiatric conditions characterized by decision-making deficits (Whitton, Treadway & Pizzigalli, 2015; Evens, Hoefler, Biber & Lueken, 2016; Deserno, Schlagenhauf, Heinz, 2016).

From a neuroimaging point of view, we found in DM1 patients, a pattern of increased functional connectivity between VTA and the left supramarginal (BA40) and superior temporal (BA41) gyri. Interestingly, these areas fall within one of the major nodes of the default mode network and, consistently with a previous study (Serra et al., 2014), it predominantly involves the left hemisphere. It is not clear why the left hemisphere appears to be predominantly affected, and further studies are needed to confirm this finding. When looking at associations between VTA-driven functional connectivity and DM1 patients' IGT net-scores, a negative correlation was found in the supplementary motor area (BA6) of both sides and in the precentral gyrus (BA4). The supplementary motor area (BA6) is an association cortex involved in the planning and sequencing of voluntary movements (Nachev, Kennard, Husain, 2008), whereas the precentral gyrus (BA4) is the primary motor cortex. An activation of BA6 and BA4 was previously described in healthy subjects (Lawrence, Jollant, O'Daly, Zelaya & Phillips, 2009) when performing the IGT in a fMRI study. Lawrence and co-workers concluded

that subjects showing a greater sensitivity to uncertainty have more careful planning of motor responses, especially during the high-risk trials (Lawrence, Jollant, O'Daly, Zelaya & Phillips, 2009). Against this background, we speculate that in DM1 patients a VTA-mediated dopaminergic overflow may produce a hyperconnectivity in BA6 and BA4, thus reducing patients' ability to anticipate the reward/punishment and learn a winning strategy. Consistent with this hypothesis, it has been previously shown that VTA dopaminergic neurons respond to the reward system (Schultz, Dayan, Montague, 1997; Brocka, et al., 2018) and play a critical role in adaptive decision-making (Richter & Gruber, 2018). Additionally, a dopaminergic overdose induced by replacement therapy was demonstrated to affect decision-making in patients with Parkinson's disease (Evans, Hoefler, Biber & Lueken, 2016).

Another point of the present results worth highlighting is that all the brain areas we found modulated by VTA connectivity and associated with IGT performance in DM1 patients are also part of the mirror neuron system (Rizzolatti & Craighero, 2004). The mirror neuron system is implicated in different aspects of social cognition (i.e., theory of mind, empathy, etc.) as well as in reward-related brain modulation (Cook, Bird, Catmur, Press & Heyes, 2014). Indeed, the neural activation related to reward is involved in the selection of the actions driven by a goal-directed behaviour (Cook, Bird, Catmur, Press & Heyes, 2014).

This study suffers from some limitations. First, the sample size was relatively small. However, this was by definition an exploratory study and DM1 is a relatively rare condition. Despite this limitation, our results were significant (as predicted by our power calculation). Second, RS fMRI is known to be potentially affected by motion artefacts and other sources of biases. We have addressed this issue by thoroughly checking our data and excluding participants with showing evidence of movement. Of

note, based upon this criterion we excluded more healthy participants than patients, suggesting that the findings cannot be explained by motion. Finally, it should be noted that the fMRI signal was regressed against the mean white matter CSF signals, which were extracted using the result of automated segmentation. It is possible that the presence of white matter lesions, a feature of DM1 (Meola & Cardani, 2015), might have affected the results of this segmentation. However, no obvious biases were observed after careful examination of the output. In addition, as white matter masks were purely used for computing the average signal, we do not expect the effect to be significant.

In conclusion, the current study indicates that a prominent deficit of decision-making in patients with DM1 might be related with an increased connectivity between VTA dopaminergic neurons and brain areas that are critical for the reward/punishment system and for social cognition. Given the small sample size, these results should be replicated in larger cohorts before generalisation. Nevertheless, these findings support the hypothesis that, in DM1, a common neurodevelopmental substrate may affect a set of higher-level functions accounting for the daily difficulties experienced by patients.

To date, the exploration of computational models of dopamine in value-based decision making has not been extensively investigated using direct pharmacological challenges in human subjects. Undoubtedly, future directions include the need to study how dopamine modulation influences the constituent components of value in human choice. Nonetheless, some evidence of efficacy of cognitive behavioural therapy on clinical symptoms in patients with DM1 has been shown by a single-blind randomised-trial (Okkersen et al., 2018). The comprehension of brain connectivity changes associated to clinically meaningful symptoms of DM1 might identify potential targets

for neurophysiological modulation, as shown in other neurological disorders (Koch et al., 2014; Koch et al., 2018).

Following the results of the current study, we hypothesize some future direction in terms of clinical trials that should be designed to identify appropriate treatments for the higher level dysfunctions observed in patients with DM1. First, specific cognitive trainings with a focus on decision-making abilities should be developed and tested for their potential to improve patients' dysfunctions and quality of life. Second, in our cohort of DM1 patients, we identified a set of cortical regions (i.e., supramarginal gyrus [BA40]; superior temporal gyrus [BA41]; supplementary motor area [BA6]; right precentral gyrus [BA4]) that might be considered as suitable targets for non-invasive brain modulation. Trials using TMS or Transcranial Direct-Current Stimulation (tDCS) should therefore be designed (in isolation or in combination with cognitive trainings) to test the efficacy of brain modulation in improving patients' dysfunctions. Finally, this work suggests a prominent role for increased VTA connectivity in determining patients' symptoms. Clinical trials should be designed to test the potential efficacy of antidopaminergic agents, which are expected to reduce the dopamine outflow. A proven efficacy of antidopaminergic drugs would confirm the causative role of VTA in determining higher level dysfunctions in DM1 patients, and would open to more invasive perspectives of treatment, such as using Deep Brain Stimulation (DBS) in selected patients who would not respond to non-invasive interventions. Although the mechanism by which DBS produces beneficial effects in neuropsychiatric conditions is still not completely understood (Chiken et al., 2016), one could hypothesize DBS strategies with the goal of inhibiting local VTA neurons.

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Competing Interests

The Authors report no competing interests

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Figure legends

Figure 1. Seed area used to assess connectivity in VTA

The figure illustrates the anatomical point used as seed to assess connectivity starting from VTA. For the anatomical definition of VTA the Harvard AAN Atlas was used (https://www.martinos.org/) (Edlow et al., 2012). For the purpose of the illustration the VTA is overlaid onto the Ch2bet template using mricron (http://people.cas.sc.edu/rorden/mricron/).

Abbreviations: AAN=Ascending Arousal Network; R= Right; VTA= Ventral Tegmental Area

See text for further details.

Figure 2. Iowa Gambling Task performances

Panel A: trial-by-trial Iowa Gambling Task performances; panel B: Iowa Gambling Task net-scores obtained by patients with DM1 (in yellow) and by healthy subjects (in blue). The asterisk indicates significant difference between groups.

Abbreviations: DM1= Myotonic Dystrophy type 1; HS= Healthy Subjects

See text for further details.

Figure 3. VTA-driven Functional Connectivity changes between DM1 patients and healthy subjects

As shown in the plots, DM1 patients compared to controls exhibited an increase of functional connectivity in the left supramarginal gyrus (BA40) and in the left superior temporal gyrus (BA41).

Abbreviations: BA= Brodmann area; DM1= Myotonic Dystrophy type 1; FC= Functional Connectivity; HS= Healthy Subjects; L= Left.

See text for further details.

Figure 4. Associations between VTA-driven Functional Connectivity and Iowa Gambling Task performance in DM1 patients.

Patients showed negative correlations (as shown by the plots) between IGT-net scores and functional connectivity in the left supplementary motor area (BA6) and in the right precentral gyrus (BA4).

Abbreviations: BA= Brodmann area; DM1= Myotonic Dystrophy type 1; FC= Functional Connectivity; L= Left; R=Right.

See text for further details.

Table 1. Principal demographic and clinical characteristics of studied subjects.

	DM1 patients N=31	**HS N=26**	**p-value**
Mean (SD) age [years]	43.7 (12.6)	45.7 (13.2)	0.864[a]
Gender (F/M)	12/19	11/15	0.782 [b]
Mean (SD) years of formal education	12.1 (2.6)	17.5 (2.8)	0.000. [a]
Mean (SD) [range] CTG triplets expansion	467 (272) [73-1200]	-	-
Mean (SD) [range] MIRS score	2.8 (0.7) [2-4]	-	-

[a] One-way ANOVA; [b] Chi-square.

Abbreviations: DM1=Myotonic Dystrophy type-1; MIRS=Muscular Impairment Rating Scale; HS=Healthy Subjects,

FIGURES

Figure 1

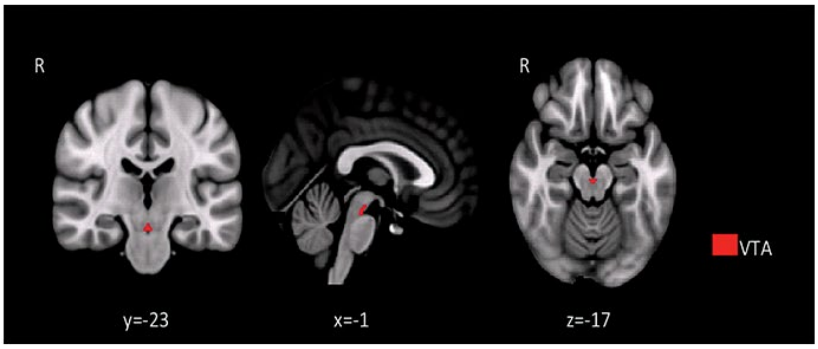


Figure 2

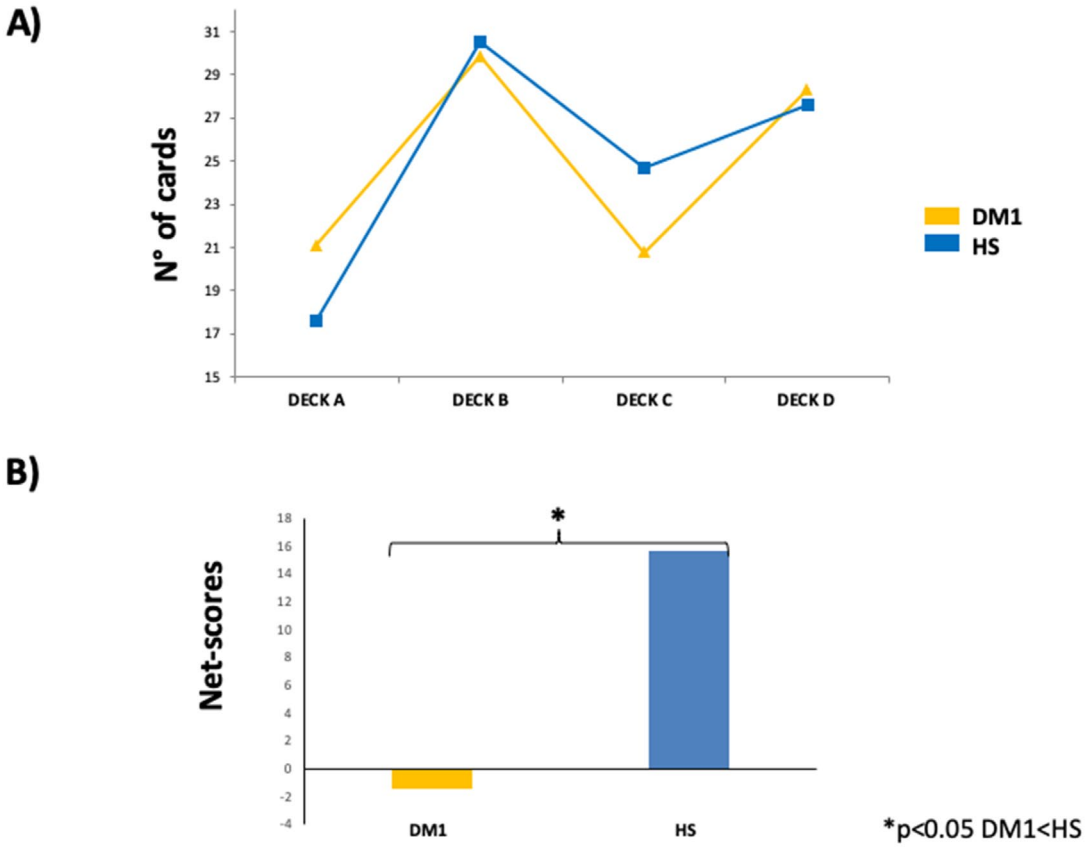

A)
N° of cards
31
29
27
25
23
21
19
17
15
DECK A
DECK B
DECK C
DECK D
DM1
HS
B)
Net-scores
18
16
14
12
10
8
6
4
2
0
-2
-4
*
DM1
HS
*p<0.05 DM1<HS

Figure 3

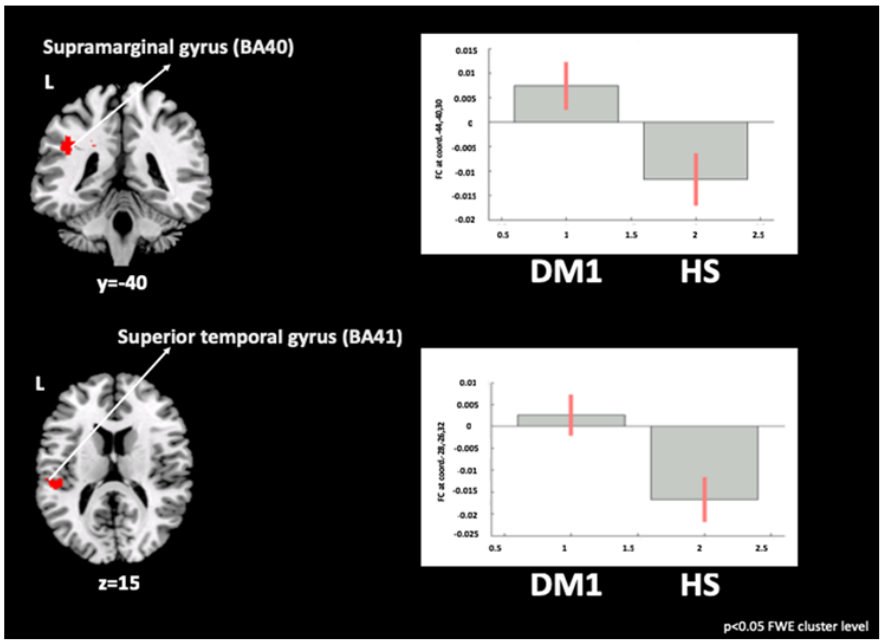
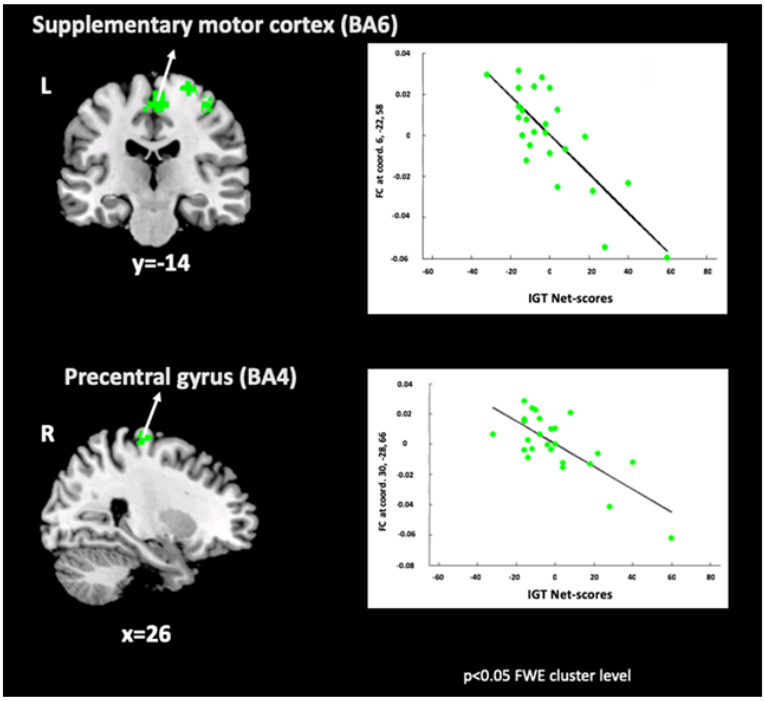

Supramarginal gyrus (BA40)
L
y=-40
Superior temporal gyrus (BA41)
L
z=15
DM1
HS
DM1
HS
p<0.05 FWE cluster level

Figure 4


Supplementary motor cortex (BA6)
L
y=-14
FC at coord. 6, -22, 58
IGT Net-scores
Precentral gyrus (BA4)
R
x=26
FC at coord. -30, -28, 66
IGT Net-scores
p<0.05 FWE cluster level