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## Viewpoint

# Social cognition in type 1 myotonic dystrophy – A mini review

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## ABSTRACT

Our ability to interact with those around us plays an important role in our relationships, mental well being and ability to successfully navigate the complex social society in which we live. Research in social cognitive neuroscience aims to understand the underlying neurobiology of our social behaviours and interactions with others. Myotonic dystrophy type 1 (DM1) is a genetically inherited neuromuscular disorder characterized by myotonia with systemic manifestations such as cardiac disease, respiratory insufficiency, ophthalmic complications, diabetes and frontal balding among others. Individuals with myotonic dystrophy have been found to have widespread changes throughout the brain in both grey and white matter territories. They have been noted to experience difficulty with social cognitive function, and to more frequently display atypical personality traits leading to often unrecognized difficulties with everyday life. In this mini review we explore the anatomical basis of social cognition, current techniques for measuring and investigating this impairment including facial emotion recognition and theory of mind. We examine the evidence for general cognitive dysfunction, autism spectrum and personality disorders in DM1. Throughout the review we discuss neuroimaging highlights relevant to social cognition in DM1. Finally, we discuss practical implications relevant to managing people with myotonic dystrophy and highlight future research needs.

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## 1. Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominantly inherited neuromuscular disorder, caused by an expansion of the trinucleotide CTG repeat motif on the DMPK gene of chromosome 19 (Brook et al., 1992). DM1 affects at least 1 in

8000 people worldwide and is the most common form of myotonic dystrophy with a clinical onset in adulthood (Emery, 1991; Meola & Cardani, 2015) DM1 is clinically characterised by myotonia, but patients commonly experience cardiac conduction defects, diabetes, gonadal hypotrophy, ophthalmic manifestations such as cataracts and raised intraocular

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pressure, gastrointestinal disease, respiratory insufficiency, frontal balding, in addition to central nervous system dysfunction (Meola & Sansone, 2007). In 1983, Bird et al. published a study examining personality and cognitive dysfunction in patients with DM1 (Bird et al., 1983). In the past thirty six years, our understanding of the cognitive profile of individuals with DM1 has been a source of energetic research interest although it still remains incompletely understood. During this time it has been observed that patients with DM1 can often perform at a comparative level with healthy controls in some aspects of IQ and cognitive testing, but many patients struggle with everyday social interaction, greatly affecting their quality of life and ability to succeed in independent living (Nätterlund et al., 2001; Serra et al., 2015). Several studies have examined social cognition and impairment as an explanation of this dichotomy.

Neuroimaging has the potential to provide a non-invasive means of exploring the possible connection between brain structure and function in DM1. A recent systematic review examining more than 80 neuroimaging studies of patients with DM1 found widespread grey matter volume reduction affecting the basal ganglia, cerebellum and all 4 cortical lobes, in addition to general atrophy. White matter hyperintensities were found in 70% of patients compared to 6% of healthy controls. Reduced glucose uptake and cerebral perfusion was demonstrated in frontal, temporal, parietal and occipital lobes, using Positron Emission Tomography (PET) imaging and magnetic resonance imaging (MRI) (Minnerop et al., 2018). More specific studies examining the relationship between personality traits/disorders have used resting-state functional MRI and suggest that abnormal connections within the default-mode network correlate with the presence of atypical personality traits, which may contribute to overall social cognitive dysfunction (Serra et al., 2015). Finally, resting-state functional MRI with a focus on ventral tegmental area (VTA) connectivity has recently pointed out a possible implication of dopaminergic abnormalities in the higher-level dysfunctions observed in DM1 individuals (Serra, Scocchia, et al., 2020).

In this short paper we aim to review the most recent developments in this area, with the aim of clarifying the most consistent findings in terms of impaired social cognition in DM1, and the most consistently reported anatomical correlates of this impairment. Finally, we identify the outstanding questions and the study designs needed to address them.

### 1.1. What is social cognition?

Social cognitive neuroscience is the branch of neuroscience which seeks to understand the neurobiology underlying our behaviour and ability to engage in social interaction. Social cognition is believed to be the mechanism by which human beings can perceive, store, retrieve and regulate information about themselves and others. It allows us to speculate how others are feeling, what they are thinking and what their intentions might be (Adolphs, 2009). It also allows us to manage emotional reactions to other people and the correct interpretation of social cue perception. In order for social cognition to function successfully, an individual must be able to decipher a vast array of social cues by correctly

understanding meaning relayed through others' facial expression, voice, body movements, including hand gestures, posture and gait (Green et al., 2015). The study of social cognition has highlighted key areas which are deemed necessary within the overall process, these include the understanding of the intention of others, the recognition of emotion, being able to follow eye gaze, shared attention mechanism and higher order theory of mind (ToM) (Frith & Frith, 1999). ToM is based on two different components, the cognitive and the affective one, the former including thoughts, intentions and beliefs, the latter involving thinking of feelings and emotions (de la Osa et al., 2016).

Neuroimaging (Frith & Frith, 2006; Adolphs, 2009; Tranel et al., 2002; Sabatinelli et al., 2011) and animal studies (Premack & Woodruff, 1978) have allowed us to attempt to localize certain areas of the brain that may be involved in particular aspects of social cognition. Interpreting actions or the intention of gaze shifts, may be linked to activity in the posterior part of the superior temporal sulcus (pSTS). This region has been shown to be active during tasks involving perspective taking and cognitive empathy (Frith & Frith, 2006). Regions of the brain such as the anterior temporal lobes, inferior occipital gyrus, infero-lateral temporo-occipital cortex, the basal ganglia, amygdala and notably the ventromedial prefrontal cortex (vmPFC) appear to be particularly involved with the perception and processing of social signals which are non-verbal (Adolphs, 2009; Tranel et al., 2002; Sabatinelli et al., 2011).

Higher order ToM describes the ability to infer 'mental states' to another individual, including their perceived motives, beliefs and knowledge, in an attempt to predict their behaviour (Frith & Frith, 2006). ToM is believed to involve two main domains, responsible for cognitive and affective ToM, with specific anatomical correlates for each domain. Cognitive ToM appears to involve the dorsal medial and lateral prefrontal cortex and the temporoparietal junctions, while affective ToM is located within the medial frontal cortex (MFC), the orbitofrontal cortex (OFC), and the inferior lateral frontal cortex (ILFC) (Abu-Akel & Shamay-Tsoory, 2011; Elamin et al., 2012). The medial prefrontal cortex (MPFC) appears to be strategically involved with the regulation and interpretation of socio-emotional states in conjunction with the OFC and ILFC.

Neuroimaging studies by Ruby et al. have shown that the ability to distinguish one's self from others, and to consider another's perspective above your own involves activation of the MPFC (Ruby & Decety, 2003, 2004). In addition to the prefrontal cortex, it is believed that the anterior cingulate cortex (ACC), the temporal pole and striatum are also involved in both affective and cognitive ToM (Abu-Akel & Shamay-Tsoory, 2011). The ventral ACC (vACC) has been shown to be associated with emotional aspects of self-reflection (Moran et al., 2006; van der Meer et al., 2010) while the dorsal ACC (dACC) is involved with processing cognitive ToM and has connections with the dorsal MPFC and the dorsolateral prefrontal cortex (Abu-Akel & Shamay-Tsoory, 2011). The temporal pole similarly has areas which appear to project to both affective and cognitive ToM active regions of the MPFC and OFC (Kondo et al., 2003).

## 1.2. Measuring social cognition in DM1

As shown in Table 1 in this brief review of social cognition in patients with DM1 we evaluated the papers considering several factors including: type of article, sample-size, study design, specific tests used to assess social cognition, assessment of cognitive functions and behavioural disorders, correlations with cognitive functions, genetic load and brain changes. We found nine original articles focused on social cognition, six of them focalised on facial emotions (Winblad et al., 2006; Takeda et al., 2009; Kawamura et al., 2009; Kobayakawa et al., 2010; Kleberg et al., 2010; Serra et al., 2020) and just three on ToM (Kobayakawa et al., 2012; Serra et al., 2016; Labayru et al., 2018). All of them were cross-sectional studies comparing DM1 patients against a group of healthy subjects. However, some studies reported small-sample sizes making the results less impacting (Takeda et al., 2009; Kawamura et al., 2009; Kobayakawa et al., 2010, 2012). Basic neuropsychological assessment was performed in all studies investigating social cognition. Instead, behavioural aspects were considered only in some of the studies (Winblad et al., 2006; Takeda et al., 2009; Kawamura et al., 2009; Kobayakawa et al., 2010, 2012). Associations with cognitive dysfunction (Winblad et al., 2006; Kobayakawa et al., 2010, 2012; Kleberg et al., 2014), genetic load (Winblad et al., 2006; Kobayakawa et al., 2010, 2012; Serra et al., 2016; Serra et al., 2020) were explored in part of the studies. Few studies investigated brain features of DM1 (Takeda et al., 2009; Kawamura et al., 2009; Kobayakawa et al., 2010; Serra et al., 2016; Serra et al., 2020), and Fig. 1 illustrates the principal brain areas involved in DM1 patients. Personality and affective disorders have been investigated in 10 different studies, one of which is a systematic review (Minier et al., 2018), while the others are original articles (Delaporte, 1998; Bungener et al., 1998; Di Costanzo et al., 2000; Meola et al., 2003; Winblad et al., 2005; Peric et al., 2014; Serra et al., 2014; Gallais et al., 2015; Bertrand et al., 2015). Three papers had an observational design, including only a group of patients with DM1 (Di Costanzo et al., 2000; Peric et al., 2014; Bertrand et al., 2015); three papers compared DM1 patients against both patients with facioscapulothoracic dystrophy (FSHD) and healthy subjects (Bungener et al., 1998; Delaporte, 1998; Gallais et al., 2015), while a study compared DM1 patients with patients with spinal muscular atrophy (SMA) and healthy subjects (Winblad et al., 2005). No study investigated cognitive functions together with personality and affective disorders, while three studies assessed the correlations with the CTG triplet's expansion size (Winblad et al., 2005; Peric et al., 2014; Serra et al., 2014). Only Serra et al. (2014) explored the associations between personality and brain changes in patients with DM1. Finally, we included here two recent revisions: one focalised on the similarities between DM1 and individuals with Autism (Angeard et al., 2018) and another focalised on the cognitive dysfunction typically observed in DM1 patients (Okkersen et al., 2017).

In the following paragraphs these studies have been reported in detail.

### 1.2.1. Facial emotion recognition

Development of tools to measure social cognition clinically has been ongoing since 1976 with the development of the Ekman 50 test of Facial Affect (Ekman, 1976). In DM1 there has

been recent work examining facial emotion recognition and eye movements as measures of social cognition, their relationship to CTG repeat expansion size and white matter disease. Using pictures from Ekman and Friesen's Pictures of Facial Affect (POFA), Winblad et al. examined the ability of DM1 patients to detect facial emotions compared to healthy controls (Winblad et al., 2006). They reported that the DM1 patients had difficulties with detecting angry, fearful and disgusted facial expressions, while they were able to detect surprise as well as controls. Fatigue, age and sex were controlled for and did not affect the significance of the results. DM1 patients appeared to mistake fear for surprise and disgust for anger, suggesting that they had some understanding of the type of emotion. This study also examined the correlation between a facial emotion recognition deficit and increasing CTG repeat expansion size, finding a significant relationship. With additional neuropsychological testing this correlation also extended to visuoconstructive ability and sociability on the Temperament and Character Inventory, suggesting that those patients with increasing impairment of recognition may also struggle with sociability (Winblad et al., 2006).

In a relatively small studies, Takeda et al., 2009 and Kobayakawa et al. investigated the ability of DM1 patients to interpret facial emotions compared to healthy controls and explored the possibility of a relationship to white matter lesion load (Takeda et al., 2009; Kobayakawa et al., 2010). The investigators first carried out a screening test to ensure that all subjects were able to discriminate faces. DM1 patients were found to be able to do this as well as healthy controls. In assessing sensitivity to facial emotion, DM1 patients were once again found to have difficulty recognising disgust and anger compared to healthy controls. There appeared to be no correlation with CTG repeat expansion size, demographic or other clinical data. White matter lesions were found predominantly in the frontal, temporal and insular region, in addition to high signal areas in the orbitofrontal cortex and anterior temporal areas. Lesions in the frontal temporal regions and insula were associated with insensitivity to detecting angry faces, while lesions in the temporal region only were associated with diminished ability to detect disgust (Kobayakawa et al., 2010). The authors highlight that all patients in the study had insular lesions, which have previously been thought to be responsible for the recognition of disgust. However, significant correlation was not found between the inability to detect disgust and insular lesions in this case (Phillips et al., 1997; Calder et al., 2000). In light of previous studies suggesting that the limbic system is involved in the recognition particularly of negative emotions such as fear and anger (Adolphs et al., 1995), the authors suggest that limbic system dysfunction, due to the presence of these white matter lesions, may account for the deficits in facial emotion recognition (Kobayakawa et al., 2010). Another study done by Kawamura et al., further demonstrated lower sensitivity to disgusted, angry and fearful faces in DM1 patients compared to controls. In addition to this, patients with a greater number of lesions in the anterior temporal lobes appeared to have decreased sensitivity to facial emotions compared to those with a lower lesion load in this region giving further evidence

**Table 1 – Studies included in the review.**

| Study area<br>Domain                  | Author/s, year                             | Article type      | Subjects' number and type  | Study design    | Test/s used to assess Social Cognition | Neuropsychological tests for the screening of cognitive functions | Test/s to assess behavioral disorders | Association with cognitive dysfunctions | Correlations with genetic load | Brain imaging           |
|---------------------------------------|--|-------------------|----------------------------|-----------------|--|---|---------------------------------------|---|--------------------------------|-------------------------|
| <b>Social Cognition</b>               |  |                   |                            |                 |  |   |                                       |   |                                |                         |
| <i>Facial emotion recognition</i>     |  |                   |                            |                 |  |   |                                       |   |                                |                         |
|                                       | <a href="#">Winblad et al., 2006 *</a>     | Original research | 50 DM1<br>40 HS            | Cross-sectional | Facial expression recognition test     | Performed   | Performed                             | Positive and negative correlation       | Negative correlation           | Not Performed           |
|                                       | <a href="#">Takeda et al., 2009</a>        | Original research | 2 DM1<br>11 HS             | Cross-sectional | Facial expression recognition test     | Performed   | Performed                             | Not Performed                           | Not Performed                  | Structural- MRI         |
|                                       | <a href="#">Kawamura et al., (2009)</a>    | Original research | 4 DM1<br>11 HS             | Cross-sectional | Facial expression recognition test     | Performed   | Performed                             | Not Performed                           | Not Performed                  | Structural- MRI & SPECT |
|                                       | <a href="#">Kobayakawa et al., (2010)</a>  | Original research | 9 DM1<br>13 HS             | Cross-sectional | Facial expression recognition test     | Performed   | Performed                             | No significant correlation              | No significant correlation     | Structural- MRI         |
|                                       | <a href="#">Kleberg et al., 2014*</a>      | Original research | 33 DM1<br>30 HS            | Cross-sectional | RBMT-E                                 | Performed   | Not Performed                         | Not Performed                           | Not Performed                  | Not Performed           |
|                                       | <a href="#">Serra et al., 2020*</a>        | Original research | 26 DM1<br>25 HS            | Cross-sectional | Social Cognition Battery               | Performed   | Not Performed                         | Not Performed                           | Negative correlation           | Structural- MRI         |
| <i>ToM</i>                            |  |                   |                            |                 |  |   |                                       |   |                                |                         |
|                                       | <a href="#">Kobayakawa et al., (2012)</a>  | Original research | 9 DM1<br>12 HS             | Cross-sectional | Faux Pas Test; RMET                    | Performed   | Performed                             | Positive correlation                    | No significant correlation     | Not Performed           |
|                                       | <a href="#">Serra et al., 2016*</a>        | Original research | 20 DM1<br>18 HS            | Cross-sectional | RMET;<br>ToM Story                     | Performed   | Not Performed                         | Not Performed                           | Negative correlation           | Functional-MRI          |
|                                       | <a href="#">Labayru et al., 2018*</a>      | Original research | 38 DM1<br>38 HS            | Cross-sectional | POFA;<br>Faux Pas Test; TECA           | Performed   | Not Performed                         | Not Performed                           | No significant correlation     | Not Performed           |
| <b>Autistic spectrum disorder</b>     |  |                   |                            |                 |  |   |                                       |   |                                |                         |
|                                       | <a href="#">Angeard et al., 2018</a>       | Review            | 175 DM1                    | –               | Not Performed                          | Performed   | Performed                             | Not Performed                           | Not Performed                  | PET & structural-MRI    |
| <b>Personality/Affective disorder</b> |  |                   |                            |                 |  |   |                                       |   |                                |                         |
|                                       | <a href="#">Delaporte, 1998</a>            | Original research | 15 DM1<br>14 HS<br>12 FSHD | Cross-sectional | Not Performed                          | Not Performed   | Performed                             | Not Performed                           | Not Performed                  | Not Performed           |
|                                       | <a href="#">Bungener et al., 1998</a>      | Original research | 15 DM1<br>11 FSHD<br>14 HS | Cross-sectional | Not Performed                          | Not Performed   | Performed                             | Not Performed                           | Not Performed                  | Not Performed           |
|                                       | <a href="#">Di Costanzo et al., (2000)</a> | Original research | 10 DM1                     | Observational   | Not Performed                          | Not Performed   | Performed                             | Not Performed                           | Not Performed                  | Not Performed           |
|                                       | <a href="#">Meola et al., 2003*</a>        | Original research | 21 DM1<br>19 DM2           | Cross-sectional | Not Performed                          | Performed   | Performed                             | Not Performed                           | No significant correlation     | SPECT                   |
|                                       | <a href="#">Winblad et al., 2005*</a>      | Original research | 46 DM1<br>37 SMA<br>31 HS  | Cross-sectional | Not Performed                          | Not Performed   | Performed                             | Not Performed                           | No significant correlation     | Not Performed           |
|                                       | <a href="#">Peric et al., (2014)</a>       | Original research | 62 DM1                     | Observational   | Not Performed                          | Not Performed   | Performed                             | Not Performed                           | Positive correlation           | Not Performed           |
|                                       | <a href="#">Serra et al., 2014*</a>        | Original research | 27 DM1<br>16 HS            | Cross-sectional | Not Performed                          | Performed   | Performed                             | Not Performed                           | No significant correlation     | Functional- MRI         |

|                         |                   |                            |                   |               |               |               |                       |                            |               |
|-------------------------|-------------------|----------------------------|-------------------|---------------|---------------|---------------|-----------------------|----------------------------|---------------|
| Gallais et al., (2015)  | Original research | 38 DM1<br>19 FSHD<br>20 HS | Cross-sectional   | Not Performed | Performed     | Performed     | Negative correlations | No significant correlation | Not Performed |
| Bertrand et al., 2015*  | Original research | 200 DM1                    | Observational     | Not Performed | Performed     | Performed     | Positive correlation  | Positive correlation       | Not Performed |
| Minier et al., (2018)   | Review            |                            | Systematic Review | Not Performed | Not Performed | Performed     | Not Performed         | Not Performed              | Not Performed |
| Okkensen et al., (2017) | Review            |                            | Meta-analysis     | Not Performed | Performed     | Not Performed | Not Performed         | Not Performed              | Not Performed |

**Basic cognitive functions**

Abbreviations: DM1 = Myotonic dystrophy type 1; DM2 = Myotonic dystrophy type 2; FSHD = facioscapulohumeral dystrophy; HS= Healthy subjects; POFA=Pictures of Facial Affect; RBMT-E = Rivermead Behavioral Memory Test-Extended version; RMET = Reading the Mind in the Eyes Test; SMA = spinal muscular atrophy. The asterisk indicates the most relevant studies. See text for further details.

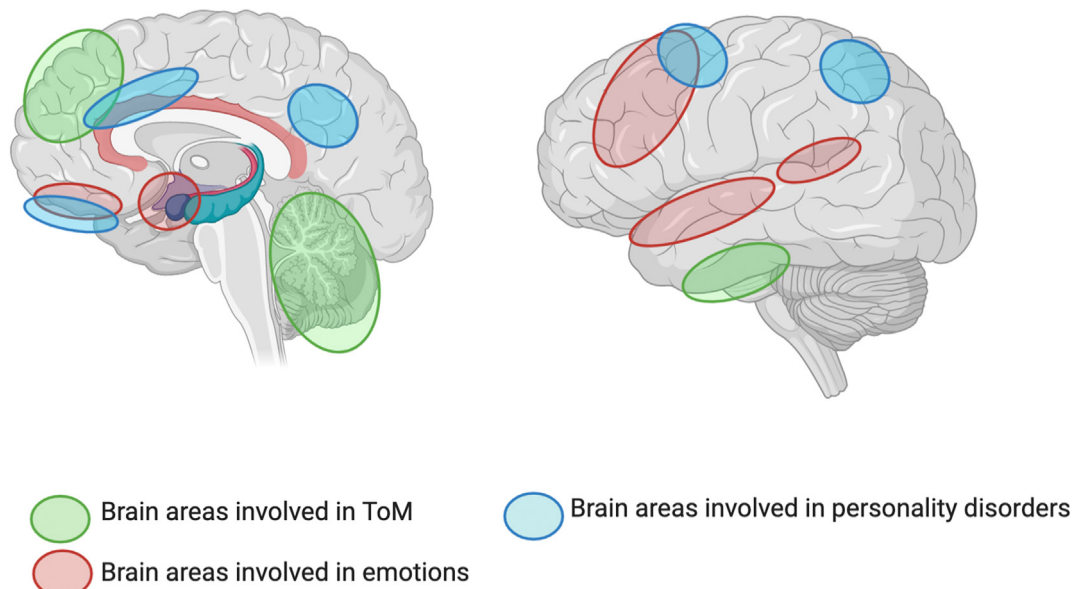
for a relationship between social cognitive function in these patients and white matter disease (Kawamura et al., 2009).

The ability to recognise facial expressions might be related to the ability to remember previously experienced ones. Indeed, the ability to remember faces or facial memory describes one's ability to remember faces which one has seen before. Many neurologists may be aware of this condition through the late British neurologist Oliver Sack's own account of his prosopagnosia or face blindness. It is a condition which may be congenital (as in Sack's case) or acquired following stroke, traumatic brain injury, infection or degenerative disease such as Alzheimer's disease. Oliver Sacks described in detail how his condition often made social interactions difficult and anxiety provoking, leading him to avoid conferences, parties and large crowds (Sacks, 2010). Kleberg et al. have examined facial memory in patients with DM1, and found that one in three DM1 patients were unable to remember faces which they had been previously exposed to. This study also found that those patients with poor facial memory struggled with tests of visuo-spatial organisation ability (Kleberg et al., 2014). A neuroimaging study of congenital prosopagnosia (Garrido et al., 2009) using voxel based morphometry, has demonstrated reduced grey matter volume in the right anterior inferior temporal lobe, the right middle fusiform gyrus/inferior temporal gyrus, the mid superior temporal sulcus (STS) and medial temporal gyrus bilaterally. Patients in this study were also tested for difficulty recognising facial emotions, but did not struggle with these tasks, suggesting an alternative pathway may be affected in those who are impaired in both (Garrido et al., 2009).

More recently, Serra et al., using a wide battery assessing several aspects of social cognition showed, in patients with DM1, a reduced ability to detect emotions correctly, such as sadness, embarrassment, happiness, and anger. Interestingly, these emotion recognition deficits were inversely associated with patients' cortical thickness in several brain areas including the right superior temporal gyrus, the precentral and angular gyri, and the medial frontal gyrus bilaterally (Serra, Bianchi, et al., 2020).

## 2. Theory of mind

Other tests of social cognitive function which focus on ToM specifically include the 'Faux Pas recognition test' which examines cognitive and affective aspects of ToM, and the 'Reading the Mind in the Eyes' test (RMET) which is more specific for affective ToM (Baron-Cohen et al., 1999, 2001). Kobayakawa et al. combined these two tests together with the aim to investigate the incidence of impaired social cognition in DM1 patients using these assessments (Kobayakawa et al., 2012). Their results showed that DM1 patients were significantly impaired with respect to faux pas recognition, in particular for the cognitive aspect of the test. The RMET highlighted a significant impairment of affective ToM for DM1 patients compared to healthy controls. However, there was a significant correlation with MMSE scores and impairment, suggesting that other forms of cognitive impairment may influence the results of this assessment (Kobayakawa et al., 2012). These findings should be taken with caution, as the



**Fig. 1** – The figure summarises the main brain areas involved in ToM (green circles), in emotional recognition (red circles) and in personality disorders (blue circles) in patients with Myotonic dystrophy type 1 (DM1). A modified version of BioRender template (<https://app.biorender.com/>) has been used to build the figure.

Faux Pas recognition test is not designed to selectively assess cognitive and affective ToM; however, other authors used the Faux pas test to assess both components (Roca et al., 2014; Bottiroli et al., 2016; Konstantakopoulos et al., 2020). By excluding patients with lower than average IQ, Labayru et al. aimed to minimise the risk of including patients with significant cognitive impairment. Although normal IQ does not exclude the presence of selective cognitive deficits, they showed that impairment in cognitive ToM is likely to be confounded by cognitive impairment in other domains (Labayru et al., 2018), as demonstrated previously (Kobayakawa et al., 2012). Their large cohort of DM1 patients had comparative level of IQ and was only found to differ significantly from healthy controls with respect to facial emotion recognition, again predominantly anger and disgust, but not with other aspects of ToM or empathy (Labayru et al., 2018). They were unable to account for the difference in scores for pictures of facial affect (POFA) between DM1 patients and controls by controlling for IQ and there was no correlation with CTG repeat expansion. A negative correlation was found between the age of the DM1 patients and their POFA score. The authors suggest that this may be in keeping with neurodegeneration as seen in other diseases such as fronto-temporal dementia (Labayru et al., 2018).

Using resting state functional MRI and whole brain analysis by graph theory, Serra et al. have investigated the possible underlying functional connectivity changes in DM1 patients (all reporting an average IQ) and existence of a ‘ToM’ network (Serra et al., 2016). Patients underwent a ToM assessment including the RMET (Baron-Cohen et al., 2001), and the ‘ToM’ test which is a story based test (ToM-story) (Baron-Cohen et al., 2001).

This study found a correlation between RMET results and CTG repeat expansion sizes. This patient cohort appeared to find the ToM-story assessment most difficult, despite normal IQ, which the authors felt may reflect difficulties with higher level executive functions. The functional MRI studies used to investigate the presence of a ToM network, identified several areas including the prefrontal, temporal, parietal, occipital and cerebellar regions which appear to sub-serve social cognitive ability. These results are in keeping with previous imaging studies exploring social cognition (Mar, 2011; Carrington & Bailey, 2009). Using the graph theory model, the authors suggest that ToM functioning is likely to depend on the connectivity between the networks, with defects in certain ‘central nodes or hubs’ contributing to more significant impairment. By further examining the central nodes using graph theory in DM1 patients compared to controls, the inferior temporal gyrus, including the fusiform gyrus was highlighted as an area of ‘high centrality’. This area was also correlated to TOMCs, a score which combines the results of RMET and ToM-story. Interestingly this study highlighted that DM1 patients showed more connections between the inferior temporal gyrus, prefrontal and cerebellar regions (Serra et al., 2016). As mentioned previously, the prefrontal cortex has been shown to play a role in social cognition (Ruby & Decety, 2003; Ruby & Decety 2012) and the posterior cerebellum and vermis have also been shown to play a role in ToM in autistic adults (D’Mello et al., 2015; Olivito et al., 2017) and schizophrenia (Mothersill et al., 2016).

Of note, the three papers that focussed on a detailed investigation of ToM in DM1 patients (Kobayakawa et al., 2012; Serra et al., 2016; Labayru et al., 2018), all employed tests

exploring both the cognitive and affective aspect of ToM (see Table 1 for more details).

### 3. Autistic spectrum disorder and DM1

Social cognition has been extensively studied with respect to autistic spectrum disorder (ASD) with impairment of emotion recognition and ToM described (Baron-Cohen, 2000). However, there is some debate about whether this is a true feature of ASD or as a result of reduced IQ (Jones et al., 2011). Several studies have questioned the possibility of comorbid ASD in congenital and childhood onset DM1. An interesting review by Angeard et al. (2018) examines this relationship as described in several studies. They note that in DM1 patients with possible ASD, as examined by Ekström et al. (2008), most display impairments of social function, and to a lesser extent, repetitive behaviours and interests seen in typical ASD (Ekström et al., 2008). This study also found that a diagnosis of ASD was usually co-existent with severe intellectual disability (ID), which can occasionally be difficult to differentiate from cognitive impairment, a common feature seen at all stages of DM1 (Vig & Jedrysek, 1999). Angeard et al. (2018) discuss the observation that both congenital and childhood onset DM1, and ASD individuals similarly exhibit a spectrum of cognitive dysfunction, yet the DM1 patients demonstrate a deficit of visual constructive function, and visual attention which is less prevalent in ASD. Imaging of both conditions (Geschwind & Levitt, 2007; Serra et al., 2016) has suggested a disconnection syndrome with primarily white matter involvement in DM1; however more comparative studies are required in order to fully understand the relationship, if any, of DM1 with ASD.

### 4. Personality disorders and features of DM1

Behaviour disturbance was noted in Steinert's first description of myotonic dystrophy (Steinert, 1909; Ambrosini & Nurnberg, 1979). A recent systematic review by Minier et al. (2018) examined the personality type, in addition to the presence of psychopathology and personality disorders in DM1 patients. They hoped to investigate whether their findings were similar to those of Ambrosini and Nurnberg who carried out a similar study in 1979 (Minier et al., 2018). Minier found that studies since this time have demonstrated that DM1 patients do not show greater evidence of psychiatric disorder than the general population. However, they did report that DM1 patients examined in these studies, while not fulfilling psychiatric diagnoses, did show evidence of mild psychopathological problems, in particular hypersensitivity, interpersonal difficulties, concern about bodily functions and dysphoria. The authors wondered if these features have had a role in difficulties in social interaction which DM1 patients experience. Personality disorders are considered a 'pervasive pattern of maladaptive traits and behaviours beginning in early life, leading to substantial personal distress or social dysfunction, or both, and disruption of others' (Tyrer et al., 2015). Two separate studies by Bungener (Bungener et al., 1998) and Delaporte (1998) found that 26.57% of adult DM1 patients met the criteria for avoidant personality disorder. Other traits that

these studies noted but to a lesser extent were paranoid, passive aggressive, obsessive compulsive and schizotypal. Another study by Meola et al. (2003) demonstrated similar results using the Structured clinical interview for disorders I and II, with patients showing significant avoidant behavioural traits but not quite meeting full criteria in this instance (Meola et al., 2003). Personality impairment, with traits associated with paranoid and dependent personality disorders predominating, were also found to be prevalent in 60% of a cohort of DM1 in a study by Peric et al. (2014).

As mentioned previously Winblad et al. (2005) have examined the relationship between facial emotion recognition and the temperament and character inventory (TCI), another tool used to assess personality traits. This group highlighted a correlation between a greater impairment of facial emotion recognition and certain traits on the TCI associated with social interaction (Winblad et al., 2005). Further work by Bertrand et al. (2015) suggested that those patients with lower CTG repeat numbers were less likely to exhibit paranoid thoughts and psychoticism that those with a greater CTG load in adult onset DM1 (Bertrand et al., 2015). Delaporte (1998) suggests that the underlying CNS disease process is a likely cause for the personality impairment experienced by DM1 patients. In a homogeneous cohort of DM1 patients with minimal muscular disability, and no previous psychiatric history they found an increased prevalence of avoidant and odd cluster personality traits compared to both healthy controls and patients with faciohumeral muscular dystrophy who experienced similar levels of muscular disability. The avoidant and odd clusters, in addition to the dependent cluster, exhibit features which Delaporte (1998) argues may overlap in principle, many of which relate to social function and interactions. In their conclusions Minier et al. (2018) also highlight the potential role of apathy in contributing to social withdrawal, potentially higher scores on depression diagnostic questionnaires and avoidant personality traits (Bungener et al., 1998; Di Costanzo et al., 2000). This theory is supported by Gallais et al. (2015), who found that 40% of DM1 patients in their cohort had clinically significant apathy, compared to patients with FSHD, which was independent of depression, functional impairment and fatigue. They speculate that the relationship between the anatomical correlates of apathy found in other neurological diseases such as lesions in the prefrontal cortex and basal ganglia (Levy & Czernecki, 2006) may also have a role to play in the apathy of DM1 patients (Gallais et al., 2015). Using PET imaging Meola et al. (2003) investigated the relationship between frontal executive function, personality traits and brain hypoperfusion in DM1 and DM2 patients. A significant correlation was found between avoidant personality traits and cerebral hypoperfusion in the frontal cortex for the DM2 patients while DM1 patients demonstrated a significant tendency towards avoidant traits compared to healthy controls. A previous study by this group with a different cohort of patients found more widespread hypoperfusion in DM1 patients, which was found to extend to the subcortical regions and dorso-lateral frontal cortex (Meola et al., 1999). The authors suggest that their findings give additional evidence for a specific behavioural and cognitive profile in both DM1 and DM2



patients. [Serra et al. \(2014\)](#) using resting-state functional MRI investigated the association between personality traits and functional connectivity in DM1 brains. Connectivity abnormalities were identified in DM1 patients compared to healthy controls within the default mode network (DMN), which is known being critically involved in cognitive as well as emotional processes. These changes of DMN connectivity were strictly associated with the presence of schizotypal personality traits in DM1 patients ([Serra et al., 2014](#)).

## 5. Cognitive function

A detailed systematic review of 40 studies by [Okkersen et al. \(2017\)](#) have found that, in addition to the global cognitive impairment evident in DM1 patients compared to healthy controls, certain domains of cognitive function may be particularly affected. Large effect sizes have been found for visuospatial perception ( $-1.01$ ) and social cognition ( $-.94$ ) ([Okkersen et al., 2017](#)). However, they advise caution in the interpretation in some of the findings from the study, due to the possibility that both aforementioned domains may rely on other areas of cognitive function such as speed of information processing and executive functions. In this review the authors also discuss the possibility that the heterogeneity of the cognitive profile may be due to the underlying CNS pathology ([Okkersen et al., 2017](#)). [Caillet-Boudin et al. \(2014\)](#) describe the current understanding of the neuropathology of DM1, which they believe to be the first disorder which exhibits features of tauopathy, RNAopathy and spliceopathy. The current view is that RNA carrying CTG expansions become trapped in the nucleus of cells in various tissues. Toxic RNA has been found in several regions and cell types of the brain of DM1 patients in addition to splicing defects ([Caillet-Boudin et al., 2014](#); [Jiang et al., 2004](#)). Deposition of toxic RNA foci in regions of the brain which are key for mediating social cognitive function and visual processing may be key to understanding this relationship further, and may give us greater understanding of the neurobiological mechanisms involved in personality and social impairments.

In summary, when considering the sample-size, the study design, the cognitive, genetic and brain evidences some of studies reported in this revision appeared particularly robust ([Winblad et al., 2005, 2006](#); [Kleberg et al., 2014](#); [Serra et al., 2020](#); [Serra et al., 2014, 2016](#); [Labayru et al., 2018](#); [Meola et al., 2003](#); [Gallais et al., 2015](#)). Other studies, although included a large number of patients, were only at an observational level reducing the impact of the inferences ([Peric et al., 2014](#); [Bertrand et al., 2015](#)). Finally, the remaining studies seem to be less consistent.

## 6. Implications of social cognitive impairment and management options

With emerging advances in the understanding of neuropathological, anatomical and neuroimaging underpinnings of social cognition in DM1, clinicians seeing patients in clinic need to remain aware of the effect of this complex impairment on the quality of life of their patients. A

Norwegian study by [Holmøy et al. \(2019\)](#) highlight that many of the social care, personal care and rehabilitation needs of patients with DM1 are being unmet. They found that patients with greater muscular impairment, and therefore more advanced disease, were most significantly affected. Using the 'Needs and provisions complexity scale', they found unmet needs in areas such as occupational therapy, physiotherapy, family carer support and personal enablers. Due to the prevalence of avoidant personality traits, apathy and global cognitive dysfunction, particularly with regards to social interaction, this questionnaire may be useful for clinicians to maintain awareness of issues which DM1 patients may not offer themselves. This study found that medical follow up was being appropriately addressed, but due to the multisystemic nature of the disease it may be difficult to ensure holistic standard of care ([Holmøy et al., 2019](#)). DM1 patients themselves have low disease awareness ([Baldanzi et al., 2016](#)) and interestingly in this study, marital status did not correlate with greater needs being met, hence it is important not to presume that the patient's partner will be aware of or able to support the needs of their partner with DM1 in the community. Awareness of the impairment of poor facial memory and emotion recognition in DM1 patients may be helpful for carers and indeed patients themselves, in developing ways of addressing anxiety and confrontation related to this. In addition to this, studies have demonstrated increased carer burden due to their lack of knowledge about the prevalence of apathy and avoidant behaviour in DM1 ([Timman et al., 2010](#); [Cup et al., 2011](#)).

To date, we were unable to find any literature describing the use of cognitive rehabilitation for social cognition in DM1 patients. Cognitive rehabilitation with a focus on social cognition is an area which is being researched in Schizophrenic patients, and may be an area which needs to be explored in DM1 ([Gordon et al., 2018](#); [Mas-Expósito et al., 2016](#)). Research investigating non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation, has shown promising results in terms of global cognitive function in patients with early Alzheimer's disease ([Koch et al., 2018](#)), and may be a useful technique to explore in DM1. Recent exploration of increased connectivity between ventral tegmental area dopaminergic neurons and areas of the brain associated with decision making and social cognition, suggests that this region may be an area of interest for future treatment based studies ([Serra, Scocchia, et al., 2020](#)). A recent single blind randomised, controlled and international trial involving 255 DM1 patients, exploring the use of cognitive behavioural therapy and optimal graded exercise plus standard care, for severe fatigue has demonstrated positive results with respect to perceived ability and social interaction ([Okkersen et al., 2018](#)). Interestingly, levels of apathy and quality of life remained stable, suggesting that further research is needed.

## 7. Conclusions

The overlap of social cognitive impairment, personality disorder, apathy and global cognitive impairment can be difficult to disentangle in patients with DM1. Increasing research in

this field is needed to shed further light on the underlying neurobiology and genetic mechanisms responsible for social cognitive dysfunction. Future studies should include comprehensive assessments of social cognition, personality traits, behavioural disorders alongside clinical and genetic variability to clarify their possible interactions. This might inform the setting up of tailored interventions in patients belonging to different subgroups. Additionally, greater understanding of how social cognition is impaired for these patients may also provide evidence of mechanisms involved in other diseases, and of how social cognition functions in health. Finally, as clinician it is important to be aware of how this impairment may affect the lives of both patients and their carers, and essential to both inform and explore ways to improve them.

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### Author contributions

Sara Leddy: Conceptualization, writing – original draft, review and editing.

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### Declaration of competing interest

The authors have no competing interests to declare.

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