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Why should neuropsychological assessment always be considered in Myotonic Dystrophy Type 2? An overview of patients' cognitive profile

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1 **Why should neuropsychological assessment always be considered in Myotonic Dystrophy**
2 **Type 2? An overview of patients' cognitive profile**
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Abstract:

Objectives and background: Myotonic Dystrophies (DM) are hereditary, multisystem, slowly progressive myopathies that also affect the central nervous system. In contrast to the well-established cognitive profile of Myotonic Dystrophy Type 1 (DM1), only few studies investigated cognitive dysfunction in Myotonic Dystrophy Type 2 (DM2), and their findings are inconsistent. We have therefore performed a formal comprehensive review of available studies in DM2 to identify the most commonly affected cognitive domains. **Methods:** An advanced search was conducted on PubMed with the terms “myotonic dystrophy type 2” AND “cognitive deficits”, “cognitive”, “cognition”, “neuropsychological”, “neurocognitive”, “neurobehavioral” in all fields. All available original research articles (13) and 1 case study, 14 in total, were included and thoroughly studied. **Results:** Most research studies indicate primary cognitive deficits in executive functions (dysexecutive syndrome), memory (short term nonverbal, verbal episodic memory), visuo-spatial/constructive-motor functions and attention while language is rarely reported to be affected. Cognitive profile is associated with brain abnormalities in several secondary and high-order cortical and subcortical regions and associative white matter tracts based on the few neuroimaging and/or multimodal studies. The limited sample size of DM2 patients is the most prominent limitation on current literature. **Conclusions:** The multifaceted profile of cognitive deficits highlights the need for routine neuropsychological evaluation in DM2 that could unveil patients’ strengths and impairments at baseline and to be carefully monitored over time.

Key words: Myotonic Dystrophy Type 2; cognitive deficits; neuropsychological assessment; neuroimaging data; clinical practice

Introduction

1 Myotonic Dystrophy (DM) is a hereditary, autosomal dominant, slowly progressive myopathy that
2 involves multiple systems and significantly affects the nervous system (Peric et al., 2017b). There are two
3 known types of DM, Myotonic Dystrophy Type 1 (DM1 or Steinert's disease) and Myotonic Dystrophy Type
4 2 (DM2) or, as it was originally named, proximal myotonic myopathy (Newman et al., 1999) or proximal
5 myotonic dystrophy (Udd et al., 1997).
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9 Patients with DM demonstrate various clinical symptoms due to muscular, cardiac, hormonal and
10 neurological involvement. The range of the clinical symptoms varies considerably from muscle
11 weakness/myotonia and early-onset cataract to cardiac arrhythmia and cognitive changes/deficits (Udd and
12 Krahe, 2012). Genetically, DM1 is caused by trinucleotide CTG repeats expansion in the 3' non-coding
13 region of the DMPK gene on chromosome 19q13.3, whereas DM2 is caused by the mutation in the intron of
14 CNBP gene on chromosome 3q21 (Meola et al., 2017, Peric et al., 2019). DM2-related symptoms are
15 considered to be milder than DM1-related symptoms, with better prognosis and later onset (Wenninger et al.,
16 2018).
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20 DM1 has been systemically and thoroughly examined with regards to CNS dysfunction and patients'
21 cognitive dysfunctions (Bajrami et al., 2017, Cabada et al., 2017). The patients' cognitive deficits seem to be
22 dependent of the symptoms onset; patients with congenital DM1 show mental retardation. In case of
23 childhood onset of DM1, learning disabilities, attention deficit/hyperactivity disorder, autistic behavior, lack
24 of interest-inhibition, and visuo-spatial impairment are commonly reported. If DM1, onset is in early
25 adulthood when patients often exhibit dysexecutive syndrome, visuospatial deficits, verbal and visual
26 memory difficulties. When the onset is at late adulthood the difficulties are mostly recognized in memory
27 (Baldanzi et al., 2016, Okkersen et al., 2017, Zalonis et al., 2010). On the other hand, there is not a clear view
28 on DM2 with only few available studies and inconsistent findings regarding DM2 neuropsychological profile
29 (Meola, et al., 2017, Meola et al., 2003, Peric, et al., 2017b). In addition to that, clinicians seem to experience
30 difficulties in successfully diagnosing DM2 patients because of unfamiliarity or inexperience with that
31 specific disorder (Meola, et al., 2017).
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35 Based on the disproportionate number of studies in DM1 and DM2 in the literature, the aim of this
36 article is to examine the cognitive deficits of the DM2 patients by identifying, evaluating, and integrating
37 research observations from recent research papers. Even though and the literature of DM2-associated
38 cognitive deficits is seemingly limited, there has been considerable progress in the field and this narrative
39 review aims to highlight these advances.
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Methods

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44 There are only a few dedicated research studies characterizing cognitive deficits of DM2 patients.
45 Accordingly, we aimed to comprehensively review all available research studies on DM2 neuropsychological
46 profile, which were published during the last twenty years, approximately, in peer-reviewed journals.
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PubMed is considered to be among the largest publically available databases for published scientific, medicine as well as neuropsychology and neurosciences-related scientific articles. We conducted multiple advanced searches during the last 12 months (the last search took place on 28st of May, 2020) including the following terms in all fields; “myotonic dystrophy type 2” AND “cognitive deficits” (92 results in total-8 for our review), “cognitive” (264 results in total-4 for our review), “cognition” (264 results in total-1 for our review), “neuropsychological” (118 results-1 for our review), “neurocognitive” (18 results in total-none for our review) and “neurobehavioral” (3 results in total-none for our review). By the aforementioned searches we excluded all papers that they focused only on DM1 patients or did not follow a methodological approach towards the evaluation of DM2 cognitive functions. Lastly, we should note that there was no need to contact the study authors to identify possible additional studies as we included every single one on that database, which were congruent with our aforementioned inclusion criteria.

In total, 14 articles, 13 research studies and 1 case study, were thoroughly studied for our narrative review. In each article we identified the cognitive domains that are primarily and secondarily affected. Moreover, we highlight specific study limitations, especially with regards to sample sizes, as well as methodology such as choice of neuropsychological instruments. Lastly, we identified common observations across multiple studies and integrate research findings to discuss the most common cognitive deficits experienced by DM2 patients.

Results

Cognitive impairment in DM2

Identifying cognitive deficits in DM2 patients is a task that takes into consideration multiple cognitive functions, including but not limited to executive functions (Peric et al., 2017a) and memory (Peric, et al., 2017b, Schneider-Gold et al., 2015, Weber et al., 2010). **We should highlight here that cognitive impairment was determined based on group comparisons between DM2 patients and healthy controls [e.g. (Gliem et al., 2019, Meola et al., 2003)] and/or specific cut-off scores that differ between studies [e.g. 1SD (Ates et al., 2019, Krogias et al., 2015, Peric et al., 2017a, Peric et al., 2015, Schneider-Gold et al., 2015) or 2 SDs (Peric et al., 2017b) below norm].** In this section we review the spectrum of cognitive functions that are affected in DM2 (Table 1).

[insert Table 1 approximately here]

Executive functions

The executive functions are the most cited facet of cognitive impairment in DM2. The frontostriatal dysexecutive syndrome is considered to be a core cognitive feature of DM2 patients (Peric et al., 2015, Peric, et al., 2017b). DM2 patients typically exhibit impaired performance on neuropsychological tests of executive functions, including the copy form of the Rey-Osterrieth Complex Figure test, the Wisconsin Sorting Card test, the Stroop Neuropsychological Screening, Semantic and Phonemic Fluency tasks, the Tower of London test, the Conditional Associative-Learning measure, the Iowa Gambling task, the Trail Making Test and executive subtests of the Cambridge Neuropsychological Test Automated Battery. This outcome is consistent with other studies that demonstrate deficits specific to frontal lobe dysfunction, such as difficulties in conditional-associative learning, decision making, planning, divided attention and attentional control, interference, alertness with and without warning signals, verbal fluency with change of categories, conceptual reasoning and set shifting (Ates et al., 2019, Meola, et al., 2003, Peric, et al., 2015, Romeo et al., 2010, Sansone et al., 2007, Sansone et al., 2006, Schneider-Gold, et al., 2015, Weber, et al., 2010).

Executive deficits have been linked to structural and metabolic brain abnormalities in a few available studies. Considerable frontal and corpus callosum white matter changes were identified and reduced fractional anisotropy in the associative fibers (i.e. bilateral superior longitudinal fasciculus) have been linked to executive dysfunction in DM2 (Minnerop et al., 2011). Moreover, tract-based spatial statistics analysis on diffusion tensor imaging data demonstrated widespread and ubiquitous white matter reduction and, interestingly, that decrease at follow-up exceeded that observed at baseline (Gliem et al., 2019). In a case study with a patient who was diagnosed both with Parkinson's disease and DM2, her executive dysfunctions were consistent with MRI findings such as diffuse white matter vascular hypodensity as well as cortical atrophy (Sansone, et al., 2006). Furthermore, brain positron emission tomography highlights a prominent impairment of glycolysis metabolism in prefrontal, temporal and pericentral regions, insula and subcortical grey matter, including basal ganglia (Peric, et al., 2017a). Of note, profound executive dysfunction has been reported in patients with hypometabolism in bilateral prefrontal and insular cortices, right parietotemporal and frontotemporal areas, as well as left striatum (Peric, et al., 2017a). Lastly, diffusion tensor imaging analyses are congruent with demonstrated executive dysfunction as they showcase a fractional anisotropy reduction in the body, isthmus and genu of corpus callosum, forceps minor, left inferior longitudinal and inferior fronto-occipital fasciculus, as well as a radial diffusivity increase in the callosal body (Gliem, et al., 2019).

Memory

Memory is a cognitive domain that is also commonly affected in DM2 (Krogias et al., 2015, Peric, et al., 2017b, Schneider-Gold, et al., 2015). Memory-related deficits are especially pronounced on tests tapping onto nonverbal (Schneider-Gold, et al., 2015, Weber, et al., 2010) and verbal (Peric, et al., 2015, Schneider-Gold, et al., 2015) episodic memory, as well as verbal and nonverbal short-term memory in general (Ates, et al., 2019). Moreover, Sansone and colleagues are the first who indicate a spatial long-term memory impairment in their case study possibly due to cortical atrophy and reduction of glucose metabolism in the parietal operculum and posterior

thalamus (Sansone, et al., 2006). Weber and colleagues used the recall form of the Rey-Osterrieth Complex Figure test and the Wechsler Memory Scale and observed nonverbal episodic memory deficits most probably due to a pronounced reduction of the grey matter in bilateral hippocampal formation (Weber, et al., 2010). In another study, Peric and colleagues detected abnormal performance on verbal episodic memory, using the recognition form of the Rey Auditory Verbal Learning test (Peric, et al., 2015).

Language

Language impairment is not classically associated with DM2. In their study, Peric and colleagues used the Boston Naming Test and the Category Fluency in order to identify language deficits (Peric, et al., 2017b). The only language impairments appeared at severe clinical phenotypes. Reduced temporoparietal metabolic activity as measured using 18F-fluoro-2-deoxy-D-glucose positron emission tomography has been related to DM2 naming deficits (Peric, et al., 2017a).

Visuo-spatial functions

Visuo-spatial dysfunctions are usually observed when visuo-spatial functions are part of the DM2 neuropsychological evaluation. Apart from executive dysfunction, Peric and colleagues described visuo-spatial dysfunctions as one of the main cognitive deficit in DM2 patients based on Wechsler Intelligence Scale Block Design subtest and the copy form of the Rey-Osterrieth Complex Figure test (Peric, et al., 2017b). Schneider-Gold and colleagues examined the visuo-spatial functions using the intelligence test Leistung - prüfungssystem subtest 7, which evaluates the spatial visualization ability, finding out impaired performance (Schneider-Gold, et al., 2015). Likewise, Sansone and colleagues indicated visuo-spatial dysfunctions using visual-spatial recall and visual-spatial construction tests (Sansone, et al., 2007). Hypoperfusion in posterior parietal lobes (Romeo, et al., 2010) might partially account for the observed visuo-spatial dysfunction. Lastly, Gliem and colleagues identified visuo-spatial dysfunctions at the Block Design Test of the HAWIE-R scale, which was linked to widespread white matter pathology, even though the authors did not find statistically significant correlations (Gliem, et al., 2019).

Attention and psychomotor speed

The above-mentioned frontal dysfunction and the involvement of white matter have been considered as one of the underlying causes for DM2 attentional deficits. The latter have been reported in different studies (Ates, et al., 2019, Gliem, et al., 2019, Meola, et al., 2003, Minnerop, et al., 2011, Sansone, et al., 2007, Sansone, et al., 2006, Schneider-Gold, et al., 2015, Weber, et al., 2010). Sansone and colleagues found both baseline and longitudinal attentional deficits that worsen over time (Sansone, et al., 2007). This progressive deterioration in frontal cognitive (attentional) impairment over time was not accompanied by deficits and/or further changes in other cognitive areas. Apparent attentional deficits have been observed in other studies as well and attributed to structural brain changes in frontal white matter, particularly association fibers, limbic system fiber tracts, callosal body and projection fibers (Minnerop, et al., 2011). Similarly, Schneider-Gold and colleagues revealed major attentional deficits in association with grey matter volume in the periaqueductal grey matter, midbrain, the bilateral thalamus (pulvinar), the bilateral parahippocampal gyrus and the anterior cingulate (Schneider-Gold, et al., 2015). Likewise, Minnerop and colleagues found reduced performance in an interference task which was

further associated with poor motor performance in a group of DM2 patients with severe frontal white matter abnormalities as well as prominent fractional anisotropy reduction in association fibers, including the bilateral superior longitudinal fasciculus, uncinate fasciculus, cingulum, fornix and anterior corpus callosum (Minnerop, et al., 2011). Reduced psychomotor speed as measured by Trail Making Test has been associated with white matter lesions mainly in centrum semiovale and subcortical frontal regions, as well as in temporal and parietal areas but to a lesser extent (Weber, et al., 2010). Furthermore, Ates and colleagues found divided attention (reaction time), tonic and phasic alertness deficits and the impaired tonic alertness, in particular, was related with significantly higher transverse relaxation time (R2*) or susceptibility in the subthalamic nucleus (Ates, et al., 2019).

Associations with patients' sociodemographic and clinical data

Few studies have examined and/or reported associations between patients' cognitive performance and sociodemographic and clinical variables. Increased age was correlated with poorer processing speed (TMT-A) (Peric, et al., 2015, Weber et al., 2010a), difficulties in set-shifting and alternation (TMT-B) (Peric, et al., 2015), errors in spatial working memory (Peric, et al., 2015) and worse immediate verbal memory (RAVLT) (Peric, et al., 2015). Longer disease duration has been related to decreased alertness (Weber et al., 2010b) and worse set shifting and alternation (TMT-B) (Peric, et al., 2015). Worse clinical status was correlated with impaired executive functions (Wisconsin Card Sorting Test) (Weber, et al., 2010b) whereas muscle strength was correlated with immediate verbal memory (Peric, et al., 2015).

Mood

Altered mood in DM2 patients is typically related to depressive symptoms which have been considered either a reactive adjustment disorder or the clinical phenotype of underlying brain abnormalities. Specifically, Minnerop and colleagues reported depression on their DM2 patients but due to the fact that it was identified in patients with less white matter pathology, they concluded that depression might be a reactive adjustment disorder often seen in the early stages of the disease and not an actual consequence of structural brain damage (Minnerop, et al., 2011). Likewise, mild and severe depressive symptoms as measured using the Beck Depression Inventory were not related to transcranial sonography findings in another more recent study (Krogias, et al., 2015). On the other hand, depression in DM2 has been associated with brainstem atrophy and the involvement of cerebellar peduncles (Schneider-Gold, et al., 2015). Lastly, a recent study demonstrates the associations of white matter changes in DM2 with clinical parameters, including depression (Gliem, et al., 2019).

Discussion

The present narrative review sought to characterize the nature of cognitive deficits of DM2 patients which are strikingly understudied compared to DM1 and are inconsistent, due to small sample sizes and the diverse methodological approaches utilized to evaluate cognitive functions. Cognitive dysfunction is apparently recognized in the majority of available studies and is often associated with brain abnormalities in several

secondary and high-order cortical and subcortical regions and associative white matter tracts, highlighting the clinical significance of neuropsychological evaluation in DM2 patients.

Cognitive dysfunctions and associated brain abnormalities

Based on few research studies that are available in regard to the neuropsychological profile of DM2 patients, we concluded that most researchers agree on the existence of cognitive deficits on the domains of executive functions, particularly set shifting, flexibility of thinking and conceptual reasoning, planning and decision making (Minnerop, et al., 2011, Peric, et al., 2017a, Peric, et al., 2015, Peric, et al., 2017b, Romeo, et al., 2010). Additional cognitive impairments were recognized in visuo-spatial/constructional dexterities (Gaul et al., 2006, Peric, et al., 2015, Peric, et al., 2017b, Romeo, et al., 2010, Sansone, et al., 2007, Schneider-Gold, et al., 2015), memory (in particular, verbal and non-verbal short-term and long-term episodic memory, as well as working memory) (Krogias, et al., 2015, Peric, et al., 2017b, Schneider-Gold, et al., 2015, Weber, et al., 2010) and attention (Minnerop, et al., 2011, Sansone, et al., 2007, Schneider-Gold, et al., 2015). Depressive mood is also commonly observed in DM2 patients (Krogias, et al., 2015, Minnerop, et al., 2011, Schneider-Gold, et al., 2015), though it is still unclear whether it is a reactive adjustment disorder (Minnerop, et al., 2011) or an actual consequence of structural brain damage (Schneider-Gold, et al., 2015).

Even though there are few multimodal studies assessing both cognitive functions and brain alterations, it seems that DM2-related cognitive impairment is associated with patients' cortical and subcortical gray matter alterations and white matter changes. The dysexecutive syndrome is associated with hypometabolism in bilateral prefrontal and insular regions, right parietotemporal and frontotemporal areas, left striatum (Peric, et al., 2017a) and with reduced fractional anisotropy in the body, isthmus and genu of corpus callosum and several frontal associative white matter tracts (Gliem, et al., 2019). In memory, the most characteristic association is that of the nonverbal episodic memory with the reduction of the grey matter in bilateral hippocampal formation (Weber, et al., 2010). As far as the language domain is concerned, it seems that reduced temporoparietal metabolic activity is correlated with naming dysfunction (Peric, et al., 2017a). Moreover, visuo-spatial dysfunctions have been linked with widespread microstructural white matter alterations (Gliem, et al., 2019). Furthermore, attentional deficits are associated with frontal white matter, particularly association fibers, limbic system fiber tracts, callosal body and projection fibers (Minnerop, et al., 2011), as well as with grey matter volume in periaqueductal grey matter, bilateral thalamus, bilateral parahippocampal gyrus and the anterior cingulate (Schneider-Gold, et al., 2015). Of note, depressive symptoms have been associated with brainstem atrophy and the involvement of cerebellar peduncles (Schneider-Gold, et al., 2015).

Clinical implications of DM2 cognitive impairment

The identification of cognitive dysfunction in DM2 may have implications for patients' daily living and caregivers' support. Most DM2 patients show executive dysfunctions which could affect planning, reasoning and/or problem solving, as everyday life requires to manage multiple different tasks. On top of that the reported attention deficits may affect concentration on discussions that take place in social interactions, as well as other daily activities that require selective attention and shift of attention between different tasks. Memory dysfunction may pose difficulties in patients' complex everyday activities, interfere with their compliance with medication

1 and engagement in rehabilitation efforts. Furthermore, the characterization of cognitive dysfunction in DM2 is of
2 utmost importance for early interventions that may allow patients and their families to deal with any cognitive
3 impairments by participating in specific cognitive rehabilitation programs. Such endeavors are lacking not only
4 in DM2 but also in DM1. However, most DM2 patients are fully capable of participating in rehabilitation
5 interventions in contrast to DM1 patients who often show severe physical deficits and significant cognitive
6 impairments. Of note, paper-and-pencil and computerized cognitive rehabilitation programs have been applied in
7 other neurodegenerative conditions with profound motor disabilities [e.g. advanced forms of multiple sclerosis
8 (Klein et al., 2017), such as primary (Prouskas, 2019) or secondary progressive (Messinis et al., 2020) multiple
9 sclerosis]. Thus, cognitive rehabilitation could be applied both in DM2 and DM1 patients

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14 Screening for cognitive deficits in DM2 is highly relevant clinically, and from an academic standpoint,
15 the detailed characterization of DM2-associated neuropsychological changes may have implications for guideline
16 development, planning of multidisciplinary interventions, and generating best practice recommendations. A
17 similar transition took place in the field of ALS a few years ago when the extra-motor profile of ALS was
18 gradually recognized (Christidi et al., 2018), increasingly supported by neuroimaging (Bede et al., 2018, Omer et
19 al., 2017) and disease-specific cognitive instruments were eventually developed (Abrahams et al., 2014, Elamin et
20 al., 2017). As detailed neuropsychological evaluation by a qualified neuropsychologist is time-consuming, brief
21 multi-domain screening tests should at least be included in the evaluation of DM2 patients at baseline and ideally
22 on follow-up assessments. It is noteworthy, that short screening instruments such as the Mini-Mental State
23 Examination might fail to detect mild cognitive deficits and lack the sensitivity and specificity to unveil executive
24 dysfunction. It is also imperative to use, population-based, local, age, and education matched normative data for
25 the interpretation of scores and account for practice effects. Other screening scales such as the Addenbrooke's
26 Cognitive Examination and the Montreal Cognitive Assessment may be sensitive to detect subtle cognitive
27 deficits. Multidomain screening instruments have been successfully validated in other patient cohorts with severe
28 motor disability, such as the Edinburgh Cognitive and Behavioral ALS Screen in amyotrophic lateral sclerosis.
29 These existing instruments could therefore be piloted in future DM2 studies and may unveil impairment in
30 cognitive domains not yet explored, such as social cognition.

31 32 33 34 **Limitations**

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46 Our narrative review is not without limitations. Firstly, it is possible that different papers published by
47 the same group (Peric, et al., 2019, Peric, et al., 2015, Peric, et al., 2017b) reported results on the same cohort.
48 Another limitation is that DM2 is not usually easily recognized due to the clinicians' inexperience with the disease,
49 so patients that ask for help and thus patients tested in cognitive studies could possibly not be the most
50 representative clinical group, as they usually are the most severe patients from the whole cohort of affected
51 patients. Moreover, the association between sociodemographic factors and cognitive performance has not been
52 studied. Additional measures that examine patients' everyday functional performance in association with their
53 cognitive performance would be of utmost importance considering that the majority of commonly used
54 neuropsychological measures show moderate association to individual's everyday performance due to the issue
55 of ecological validity of neuropsychological measures (Chaytor and Schmitter-Edgecombe, 2003).
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Conclusions

In summary, DM2 is an inherited, multidimensional disease that affects the human brain. There is not a specific DM2 neuropsychological profile, as there are only a few research studies about DM2 cognitive deficits, offering vague, even controversial, and limited information. This narrative review demonstrated the most commonly affected cognitive domains in DM2 (especially executive functions, visuo-spatial/constructive functions, attention and episodic memory) and recommended future directions, such as use of larger sample sizes, development of novel and thorough methodology so as to identify the DM2 cognitive deficits, conduction of research studies that investigate cognitive functions and brain changes, as well as identification of domains that were not previously assessed (i.e. social cognition). There is great room for research that will form the DM2 neuropsychological profile, leading also to a great contribution to how experts should use that knowledge on the cognitive rehabilitation domain of those patients. The multifaceted profile of cognitive deficits highlights the need of neuropsychological evaluation in DM2 clinical practice that could unveil patients' strengths and impairments at baseline and serve as a possible prognostic factor for monitoring disease progression over time.

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15 **Figure legends**
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19 **Figure 1.** Selection of relevant research articles for review
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Table 1. Representative studies on cognitive dysfunction in DM2 patients

Study	Authors (Year)	Sample size (DM2/HC)	Cognitive domains examined	Neuropsychological measures	Supportive Neuroimaging data	Main DM2-associated cognitive deficits
#1	Meola et al. (2003)	19 DM2 / 20 HC	Global cognitive status, Frontal functions; serial ordering, alternation, concept formation, set shifting, planning and problem solving, lexical retrieval, attention; attentional control and response inhibition	MMSE, WCST, SNST, TMT, Lexical retrieval in response to phonological and semantic cues, TLT	Yes	Executive functions (planning, conceptual reasoning, set shifting), attentional control
#2	Gaul et al. (2006)	21 DM2 / 21 HC	Mood, frontal functions, visuo-spatial functions, spatial memory, attention, verbal fluency	Profile of Mood States, ROCF, unforewarned recall procedures, symbol digit, oral word association, CAL, IGT	No	Executive functions (decision making, verbal fluency), conditional-associative learning, visuo-spatial-constructional ability

#3	Sansone et al. (2006)	1 DM2 / 0 HC	Nonverbal reasoning, auditory language comprehension, verbal fluency with phonemic and semantic cues, verbal and spatial short-term memory, verbal and spatial long-term memory, constructional abilities, alertness and divided attention, executive functions, dementia screening	MMSE, RSPM, Token test, Digit span forward, Spatial span, Story recall, Rey recall, Rey's complex copy, TMT-A & B, TLT, WCST	Yes	Spatial long-term memory, attention, executive functions
#4	Sansone et al. (2007)	17 (baseline) and 11 (follow-up) DM2 / 0 HC	Global cognitive status, nonverbal reasoning, auditory language comprehension, verbal fluency, verbal and spatial short term memory, verbal and spatial long term memory, constructional abilities, attention and executive function	MMSE, RSPM, Token test, Verbal fluency with phonemic and semantic cues, Digit span forward, Spatial span, Story recall, Rey recall, Rey's complex	No	Executive functions, alertness, divided attention, visuospatial recall, constructional ability, auditory language comprehension

				story, TMT-A & B, TEA, TLT		
#5	Romeo et al. (2010)	14 DM2 / 44 HC	Nonverbal intelligence, frontal executive functions, memory, learning functions, visuospatial abilities	RSPM, SCWT, Fluency tests, Wechsler memory scale, Corsi's block tests, ROCF	Yes	Executive functions, visuo-spatial-constructional ability
#6	Weber et al. (2010)	9 DM2 / 31 HC	Global cognitive status, crystalline intelligence, visuo-spatial abilities, dementia screening, memory, constructive abilities, planning, executive functions, verbal and nonverbal working memory, nonverbal episodic memory, learning functions, abstract reasoning and problem-solving ability, verbal short term and long term memory, alertness,	MMSE, SANFT, Vocabulary test, Clock, ROCF (copy and recall), Wechsler memory scale, Corsi block span, WCST, Digit span, Verbal fluency, Verbal learn and memory test (first and long-term recall), Alertness test (with	Yes	Global cognitive status, executive functions, nonverbal episodic memory, alertness, psychomotor speed

			attention, visual attention, psychomotor speed and task switching, mood; depression	and without warning), Divided attention, TMT, Self-administered depression rating scale, BDI		
#7	Minnerop et al. (2011)	22 DM2 / 22 HC	Focused attention, interference, motor function, psychomotor speed, attention shift and mental flexibility, naming, phonemic and semantic fluency, visuospatial/Visuoconstructive abilities, reaction time, choice reaction time, verbal memory-recognition, figural memory-recognition, mood; depression, fatigue, daytime sleepiness	c.I.T.S, c.I.T.I, Pegboard Puzzle, TMT A & B, BNT, Phonemic and semantic fluency tasks, Block test, NeurocogFX, BDI, KFSS, PSQI, Daytime Sleepiness Scale	Yes	Focused attention, interference, psychomotor speed

#8	Krogias et al. (2014)	14 DM2 / 31 HC	Selective and divided attention, simple reaction ability/alertness, nonverbal intellectual ability, flexibility of thinking, verbal shortterm memory, nonverbal shortterm memory, spatial visualization ability, nonverbal memory, dementia screening, mood; depression, daytime sleepiness	D2-test, TAP, LPS subtest 3, RWT, Digit span forwards and backwards, Block tapping forward and backwards, Visual reproduction test, RAVLT, Clock, BDI, ESS	Yes	Nonverbal short-term memory, depressive symptoms
#9	Peric et al. (2015)	34 DM2 / 0 HC	Global cognitive status, general intellectual level, verbal memory; immediate and delayed, visuo-spatial-constructural ability and visual memory, speed and attention, executive functions, verbal fluency; phonetic and semantic	CANTAB; MOT, PRM, SRM, IED, SOC, SSP and SWM, MMSE, ACE-R, RSPM, WAIS-R; Digit span and Block design, RAVLT, ROCF, TMT-A & B,	No	Executive functions, verbal episodic memory, visuo-spatial-constructural ability

				WCST, BNT, PF and SF		
#10	Schneider-Gold et al. (2015)	16 DM2 / 33 HC	Selective and divided attention, simple reaction ability, nonverbal intellectual ability, flexibility of thinking, verbal short-term memory, nonverbal short term memory, long term verbal memory, spatial visualization ability, general intelligence, dementia screening, daytime sleepiness, mood; depression	D-2 test, TAP, LPS subtest 3, RWT, Digit span forward and backward, Block-tapping forward and backward, RALVT, Multiple choice vocabulary, Clock, ESS, BDI	Yes	Memory (verbal and nonverbal short-term) , attention, executive functions, visuo-spatial-constructional ability, depressive symptoms
#11	Peric et al. (2017)	46 DM2 / 0 HC	General intellectual level, global cognitive status, visuo-spatial functions, executive functions, attention, memory, language	RSPM, MMSE, ACE-R, WAIS-R; Digit span and Block design, RAVLT, ROCF, TMT-A & B, WCST, BNT, SF	No	Visuo-spatial-constructional ability, executive functions, verbal memory

#12	Peric et al. (2017)	13 DM2 / 0 HC	Global cognitive status, verbal memory; immediate and delayed, visuo-spatial-constructional functions, visual memory, speed and attention, executive functions, language	MMSE, RAVLT, ROCF, TMT-A & B, WCST, BNT	Yes	Executive functions, naming
#13	Ates et al. (2019)	12 DM2 / 29 HC	Selective and divided attention, tonic and phasic attention; simple reaction ability, nonverbal intellectual ability, executive functions; flexibility of thinking, verbal short-term memory, nonverbal short-term memory, verbal memory, spatial visualization ability, general intelligence, dementia screening, mood; depression, daytime sleepiness	ESS, d2-Test, Go/no-Go test (TAP), LPS-Subtest 3, RWT, WMS-R, RAVLT, LPS-Subtest 7, Multiple choice vocabulary, CDT, BDI-II	Yes	Attention, executive functions, memory (verbal and nonverbal short-term)

#14	Gliem et al. (2019)	16 DM2 / 17 HC	Verbal and figural memory, semantic memory, reaction and processing speed, selective attention and reaction time, executive functions, visuo-constructive abilities, phonemic verbal word fluency, semantic verbal word fluency, mood; depression, daytime sleepiness, sleep quality, fatigue, narcolepsy	NeuroCogFX, BNT, c.I.T.I, Block design test (HAWIE-R), reaction time test, choice reaction time test, LPS-Subtest 6, BDI, PSQI, ESS, DSS, KFSS, UNS	Yes	Executive functions (interference), visuo-spatial-constructural ability, focused attention, depressive symptoms
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Note. DM2 = Myotonic Dystrophy Type 2; HC = Healthy controls; MMSE = Mini Mental State Examination; WCST = Wisconsin Card Sorting Test; SNST = Stroop Neuropsychological Screening Test; TMT = Trail Making Test; TLT = Tower of London Test; ROCF = Rey-Osterrieth Complex Figure; CAL = Conditional-Associative Learning; IGT = Iowa Gambling Test; RSPM = Raven Standard Progressive Matrices; TEA = Test of Everyday Attention; SCWT = Stroop Color and Word Test; SANFT = word test for the German word “sanft”; BDI = Beck Depression Inventory; PSQI = Pittsburgh Sleep Quality Index; ESS = Excessive Daytime Sleepiness; c.I.T.S. = Cerebraler Insuffizienztest (symbol counting); c.I.T.I. = Cerebraler Insuffizienztest (response inhibition); BNT = Boston Naming Test; KFSS = Krupp’s Fatigue Severity Scale; LPS = Leistung-sprüfsystem; RWT = Regensburger Wortflussigkeits Test; RAVLT = Rey Auditory-Verbal Learning Test; CANTAB = Cambridge Neuropsychological Test Automated Battery; MOT = Motor Screening Test; PRM = Pattern Recognition Memory; SRM = Spatial Recognition Memory; IED = Intra/Extradimensional Set Shift; SOC = Stockings of Cambridge; SSP = Spatial Span; SWM = Spatial Working Memory; ACE-R = Addenbrooke’s Cognitive Examination-Revised; WAIS-R = Wechsler Adult Intelligence Scale-Revised; PF = Phonemic Fluency; SF = Semantic Fluency; DSSDSS = Daytime

Sleepiness Scale; HAWIE-R = Hamburg-Wechsler Intelligenztest für Erwachsene-Revision; UNS = Ullanlinna-Narcolepsy Scale; TAP = Test for Attentional Performance; CDT = Clock Drawing Test; WMS-R = Wechsler Memory Scale-Revised

