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CNS manifestations in myotonic dystrophy type 1 (DM1)

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DM1 is a multi-systemic disease with significant and progressive CNS involvement

DM1 is a multi-systemic disease that presents with muscular and non-muscular signs and symptoms

Non-muscular

Muscular

- Skeletal, cardiac, and smooth muscle
  - Muscle weakness (94%)[1]
  - Myotonia (88%)[1]
  - Cardiac involvement (~50%)[2,3]
  - Respiratory impairment (71%)[4]
  - Gastrointestinal involvement (91%)[5]

CNS

- Cognitive impairment (>50%)[6]
- Behavioral/personality issues (~50%)[1]
- Emotional issues (>60%)[1]
- Excessive daytime sleepiness (93%)[1]
- Fatigue (93%)[1]

Other

Non-muscular and non-CNS manifestations, including (but not limited to):

- Cataracts[7]
- Male infertility[8]
- Endocrine abnormalities[8]
- Increased rates of certain cancers[7]

A therapy that targets both muscle and CNS symptoms is optimal[9,10]

"I'll try anything to slow it down or stop it."

"I hope, beg and pray for a drug or therapy that will help all the brain-related symptoms that DM1 patients are experiencing"

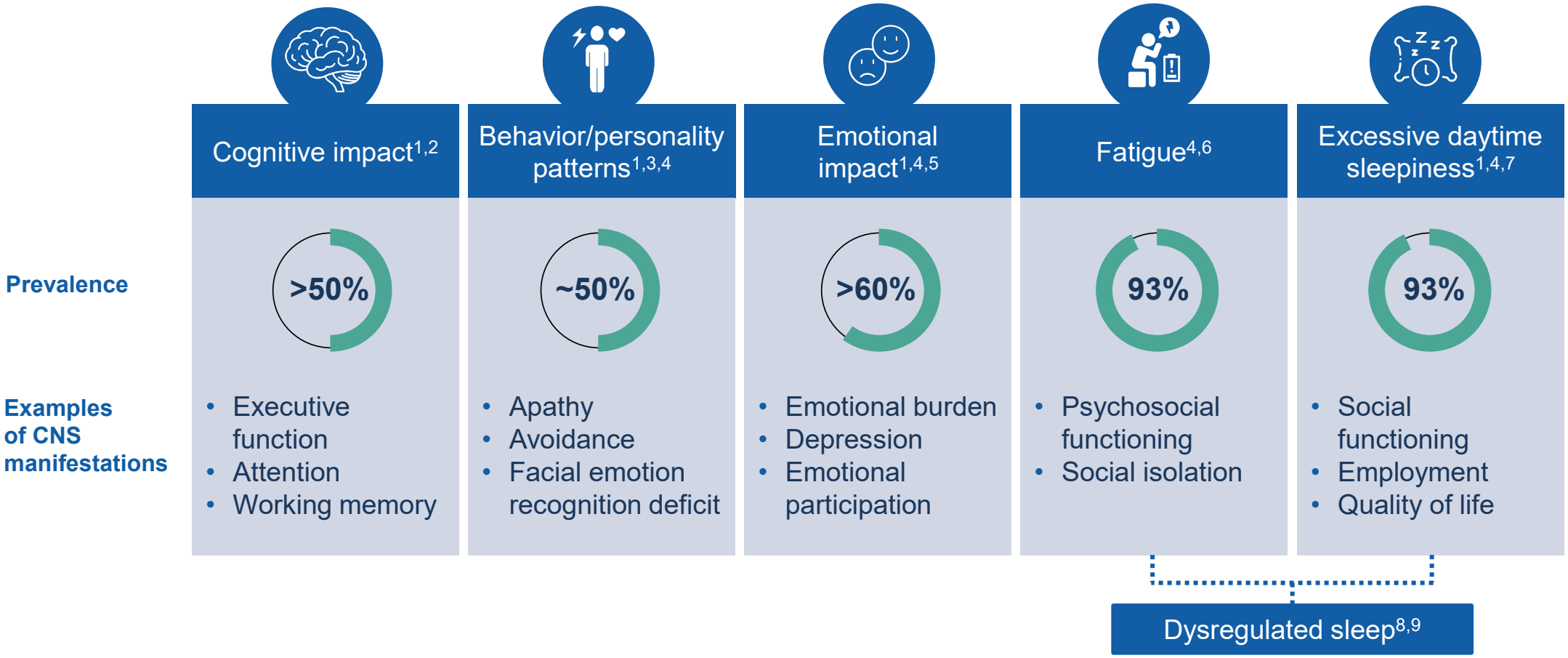
Individual with adult-onset DM1[9]

Individuals living with DM1 report considerable physical and cognitive symptoms, marking a significant unmet need[1]

CNS, central nervous system; DM1, myotonic dystrophy type 1.

1. Hagerman KA, et al. *Muscle Nerve*. 2019;59(4):457–464; 2. Petri H, et al. *Int J Cardiol*. 2014;174:31–36; 3. Groh WJ, et al. *Muscle Nerve*. 2011;43(5):648–651;
4. Hartog L, et al. Front Neurol. 2021;12:658532; 5. The Christopher Project. Report to the Myotonic Dystrophy Community. Accessed March 16, 2026. https://christopherproject.org/community_report;
6. Fujino H, et al. *Muscle Nerve*. 2018;57(5):742–748; 7. Wenninger S, et al. *Front Neurol*. 2018;9:303; 8. Winters SJ. *J Clin Endocrinol Metab*. 2021;106(10):2819–2827;
9. White M. *Ther Innov Regul Sci*. 2020;54(5):1010–1017; 10. Jimenez-Moreno AC, et al. *Patient*. 2021;14(5):601–612.

CNS involvement in DM1 is common yet heterogeneous



Almost every individual with DM1 experiences some form of CNS involvement[1,10]

CNS, central nervous system; DM1, myotonic dystrophy type 1.

1. Meola G, et al. *Muscle Nerve*. 2007; 36(3):294–306; 2. Fujino H, et al. *Muscle Nerve*. 2018;57(5):742–748; 3. Winblad S, et al. *J Neurol Neurosurg Psychiatry*. 2006;77(2):219–223;
4. Hagerman KA, et al. *Muscle Nerve*. 2019;59(4):457–464; 5. Minier L, et al. *J Neuromuscul Dis*. 2018;5(3):279–294; 6. Winblad S, Lindberg C. *BMC Neurol*. 2019;19(1):45;
7. Laberge L, et al. *Curr Neurol Neurosci Rep*. 2013;13(4):340; 8. Subramony SH, et al. *Muscle Nerve*. 2020;62(3):309–320; 9. Hamilton MJ, et al. *Neuromuscul Disord*. 2022;32(5):377–389;
10. Wenninger S, et al. *Front Neurol*. 2018;9:303.

CNS manifestations vary by DM1 clinical phenotype

CNS symptoms and features	DM1 phenotype based on age of onset		
	Congenital (at birth)*	Childhood*	Adult
Impaired executive functions (cognition)[1]	+	+	+
Cognitive decline (cognition)[1]	–	–	+
Apathy (personality/behavior)[1]	–	–	+
Anxiety (emotion)[1]	+	+	+
Fatigue[1]	+	+	+
Excessive daytime sleepiness[1]	+	+	+
Sleep disruption/dysregulation[2,3]	+	+	+

*As assessed in young individuals living with DM1. Childhood comprises infantile (up to 10 years) and juvenile onset (up to 20 years). Children and adolescents with DM1 develop symptoms of adult-onset form with age.

Congenital DM1: cognitive impairment typically presents as neurodevelopmental and intellectual issues[4]

Childhood-onset DM1: learning difficulties rather than skeletal muscle impairment are the most frequent initial symptoms[5]

Adult-onset DM1: cognitive decline is progressive, resembling accelerated aging[6–8]

Variability in clinical manifestations, age of onset, and severity complicates the evaluation of CNS symptoms in DM1[9,10]

CNS, central nervous system; DM1, myotonic dystrophy type 1.

1. De Serres-Berard T, et al. *Neurobiol Dis*. 2021;160:105532; 2. Trucco F, et al. *J Clin Med*. 2024;13(18):5459; 3. Laberge L, et al. *Sleep Med*. 2026;108781; 4. Modoni A, et al. *JAMA Neurol*. 2004;61(12):1943–1947; 5. Rahm L, et al. *Nat Rev Neurol*. 2025;21(11):623–641; 6. Winblad S, et al. *Eur J Neurol*. 2016;23(9):1471–1476; 7. Gallais B, et al. *Neuromuscular Disord*. 2017;27(1):61–72; 8. Meinke P, et al. *Front Neurol*. 2018;9:601; 9. Okkersen CP, et al. *Cortex*. 2017;95:143–155; 10. Simoncini C, et al. *Front Neurol*. 2020;11:624.

CNS involvement in DM1 is driven by spliceopathy

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CTG trinucleotide repeat expansion in the 3' UTR of the *DMPK* gene sequesters MBNL proteins leading to widespread spliceopathy[1–4]

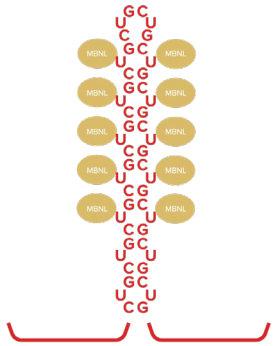
In individuals living with DM1, the *DMPK* gene contains ≥50 CTG repeats[1]

Unaffected individuals: n=5–34
Premutation: n=35–49
DM1: n>50

DMPK gene — $(CTG)_{50\ to\ >1000}$ → *DMPK* RNA $(CUG)_n$

mRNA transcribed from the mutated *DMPK* gene is retained in the nucleus, where it forms stable hairpin loops[4–6]

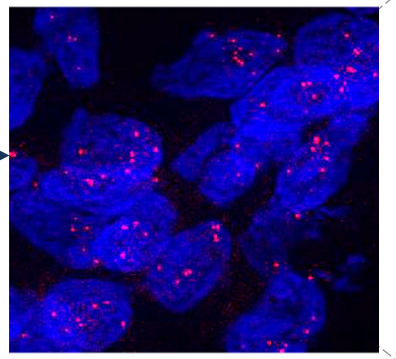
Hairpin loop with MBNL sequestration (loss-of-function)[5,7]



DMPK 3'-UTR

The stable hairpin loops sequester members of the muscleblind-like (MBNL) family of proteins, critical regulators of alternative splicing, leading to the formation of toxic nuclear foci[5,7]

Mutant *DMPK* RNA nuclear foci in human DM1 fetal samples[8]



CTG repeat ($[CAG]_5$ probe)
Nucleus (DAPI)

CAG, cytosine-adenine-guanine; CTG, cytosine-thymine-guanine; DAPI, 4′,6-diamidino-2-phenylindole; DMPK, dystrophia myotonica protein kinase; DM1, myotonic dystrophy type 1; MBNL, muscleblind-like; mRNA, messenger ribonucleic acid; UTR, untranslated region.

1. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed).* 2020;35:185–206; 2. Thornton CA. *Neurol Clin.* 2014;32:705–719; 3. Davis BM, et al. *Proc Natl Acad Sci USA.* 1997;94:7388–7393; 4. López-Martínez A, et al. *Genes (Basel).* 2020;11(9):1109; 5. Chau A, Kalsotra A. *Dev Dyn.* 2015;244:377–390; 6. Napierala M, Krzyzosiak WJ. *J Biol Chem.* 1997;272:1079–1085; 7. Misra C, et al. *Adv Neurobiol.* 2018;20:213–238; 8. Michel L, et al. *PLoS One* 2015;10:e0137620.

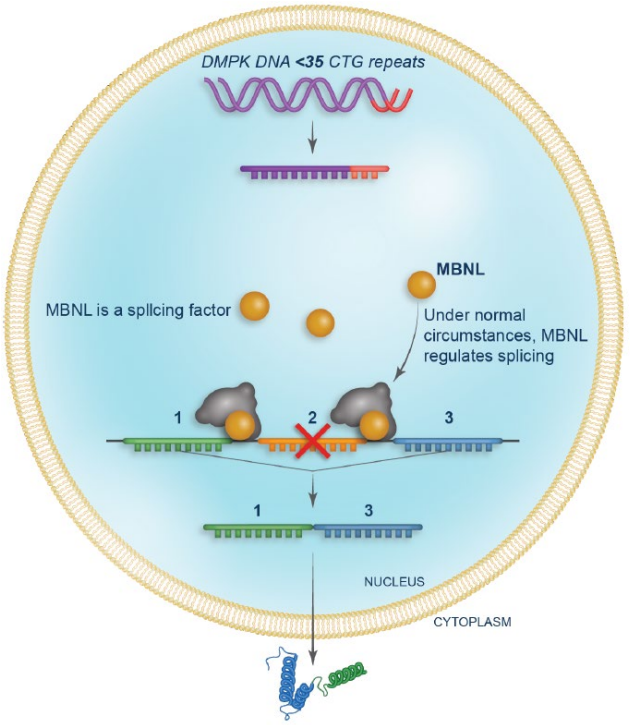
Sequestration of MBNL1 in muscle and MBNL2 in the brain results in spliceopathy

In DM1, sequestration of members of MBNL family of RNA-binding proteins leads to spliceopathy in muscle and brain[1,2]

MBNL1
- Enriched in muscle and brain[3]
- Established as a prominent RNA-binding protein retained in nuclear foci in DM1 muscle[4]

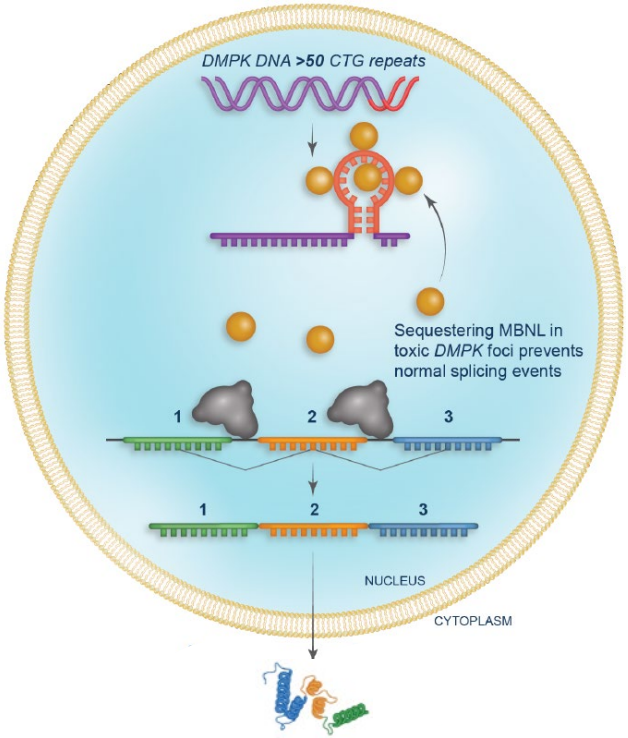
MBNL2
- Enriched in brain[5]
- MBNL2-knockout mice show:[6,7]
  - Dysregulated gene splicing
  - DM-associated CNS features (including abnormal REM sleep propensity)
  - An absence of obvious muscle manifestations and structural changes

Unaffected individuals[8]



Unaffected splicing leads to **appropriate protein synthesis**

DM1 spliceopathy[8]



Disrupted splicing **impairs protein synthesis**

MBNL sequestration leads to dysregulated alternative gene splicing[1]

Images used with permission of Sage Publications, from Berglund JA, et al. *J Neuromuscul Dis.* 2025:22143602251365101. Epub ahead of print; permission conveyed through Copyright Clearance Center, Inc.
CNS, central nervous system; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; MBNL, muscleblind-like; REM, rapid eye movement; RNA, ribonucleic acid.
1. Thornton CA. *Neurol Clin.* 2014;32(3):705–719; 2. Davies BM, et al. *Proc Natl Acad Sci USA. 1997*;94:7388–7393; 3. Zhou H, et al. *Cell Commun Signal*. 2025;23(1):97; 4. Pettersson OJ, et al. *Nucleic Acids Res*. 2015;43(4):2433–2441; 5. López-Martínez A, et al. *Genes (Basel)*. 2000;11:1109; 6. Charizanis K, et al. *Neuron*. 2012;75(3):437–450; 7. Khandelwal A, et al. *iScience*. 2023;26(5):106732; 8. Berglund JA, et al. *J Neuromuscul Dis*. 2025:22143602251365101.

Transcriptomic analyses reveal global changes that may potentially drive CNS pathology

Human brain tissue from autopsy

Misspliced gene	Brain region	Gene function	Potential CNS pathology
MAPT[1,2]	Frontal cortex Limbic area	Tau protein	Primary age-related tauopathy (PART)-like degeneration of brain tissue
NMDAR1[3–5]	Temporal cortex	Synaptic transmission and plasticity	Learning and memory
GRIP1[1]	Frontal cortex	Synaptic scaffolding	Reduced synaptic plasticity
DLGAP1[1,6]	Frontal cortex	Synaptic scaffolding	Altered synaptic transmission
KCNMA1[1,7,8]	Frontal/temporal cortex	Ion channel function	Altered neuronal activity
CSNK1D[1,7,9]	Frontal/temporal cortex	Kinase	Circadian rhythm disruption
GABRG2[1,10]	Frontal cortex	Neurotransmitter receptor	Dysregulation of GABA sensitivity

Mouse brain tissue models

Misspliced gene[7]	Role in CNS[6*]
Mapt	Microtubule-associated protein tau. Binds DNA, microtubules and protein kinase. Implicated in Alzheimer's disease
Grin1 (NMDAR1)	Glutamate receptor. Involved in synaptic plasticity, upstream of learning and memory
Ryr2	Ryanodine receptor 2. Part of calcium channel complex, expressed in several tissues including brain, plays a role in regulating heart contraction
Cacna1d	Calcium channel subunit. Plays a role in heart and smooth muscle contraction and in the transmission of auditory information
Csnk1d	Casein kinase 1, delta. Potential role in circadian rhythm
Spna2	Involved in actin cytoskeleton organization. Implicated in hereditary motor neuronopathy and epileptic encephalopathy
St3gal3	Implicated in autosomal recessive intellectual developmental disorder and epileptic encephalopathy
Tanc2	Predicted to be active in dendritic spine, glutamatergic synapse, and postsynaptic density. Implicated in intellectual developmental disorder with autistic features and language delay, with or without seizures
Ndrg4	Involved in several processes, including regulation of endocytic recycling; vesicle docking and visual learning
Kcnma1	Enables ion channel activity. Acts upstream of or within several processes, including adult walking behavior, cell maturation, and eye blink reflex

*Information taken from corresponding *mus musculus* NCBI gene database entries for each gene listed.

CNS, central nervous system; GABA, gamma-aminobutyric acid.

1. Otero BA, et al. *Cell Rep*. 2021;34:108634; 2. Hamasaki H, et al. *J Neuropathol Exp Neurol*. 2022;82(1):29–37; 3. López-Martínez A, et al. *Genes (Basel)*. 2020;11(9):1109; 4. Jiang H, et al. *Hum Mol Genet*. 2004;13(24):3079–3088; 5. Jewett BE, Thapa B. Physiology, NMDA Receptor. [Updated 2022 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519495/; 6. NIH National Library of Medicine. Gene database. Available from: https://www.ncbi.nlm.nih.gov/gene/; 7. Charizanis K, et al. *Neuron*. 2012;75(3):437–450; 8. Bailey CS, et al. *J Gen Physiol*. 2019;151(10):1173–1189; 9. Eng GWL, et al. *PLoS One*. 2017;12(5):e0177834; 10. Edokpolor KS, et al. *eNeuro*. 2022;9(5):ENEURO.0218–22.2022.

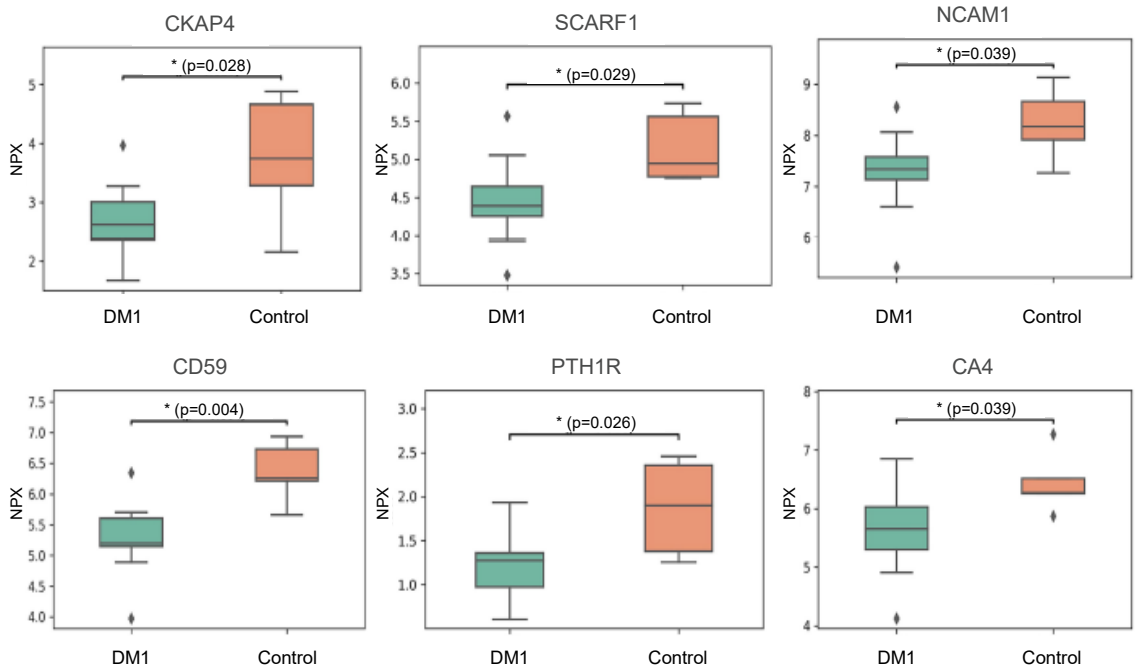
Human CSF proteomic profiling: cognitive and neurodegenerative pathology in DM1 compared to controls

Human CSF proteomic profiling

Downregulated proteins	Brain region	Protein function	Potential CNS pathology*
CKAP4[1,2]	Vascular smooth muscle cells	Cytoskeletal protein	Cognitive impairment Neuroinflammation
SCARF1[1,3]	Endothelial cells	Transmembrane “scavenger” protein	Neuroinflammation
NCAM1[1,4]	Synapses	Neural Cell Adhesion Molecule 1	Cognitive and memory deficits
CD59[1,5]	Widespread (including cortex and hippocampus)	Complement regulator	Inflammation and neurodegeneration
PTH1R[1,6]	Widespread	Parathyroid Hormone Receptor Type 1	Memory and learning
CA4[1,7]	Cerebral capillaries	Carbonic Anhydrase 4, pH balance in CNS	Memory and learning

*Potential CNS pathology may be indirectly inferred from evidence showing protein involvement in other diseases with CNS pathology and/or preclinical studies in animals.

Significant differences in protein expression between DM1 and control groups[1]



Proteins identified by CSF profiling may serve as candidates for further research into the link between protein expression changes and functional outcomes in DM1[1]

Figure from Zafarullah M, et al. *Front Neurosci.* 2025;19:1709678, licensed under a CC-BY Creative Commons license; doi: 10.3389/fnins.2025.1709678.
CNS, central nervous system; CSF, cerebrospinal fluid; DM1, myotonic dystrophy type 1; NPX, normalized protein expression.
1. Zafarullah M, et al. *Front Neurosci.* 2025;19:1709678; 2. Razzaq TM, et al. *J Biol Chem.* 2003;24;278(43):42679–42685; 3. Wang Y, et al. *eLife.* 2024;13:RP93428; 4. Duncan BW, et al. *Front Cell Dev Biol.* 2021;9:625340; 5. Yang LB, et al. *J Neurosci.* 2000;20(20):7505–7509; 6. Dettori C, et al. *J Pers Med.* 2023;13:714; 7. Blandina P, et al. *J Enzyme Inhib Med Chem.* 2020;35(1):1206–1214.

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Changes within the CNS contribute to a range of progressive CNS symptoms in individuals living with DM1

Imaging tools are insufficient in determining disease stage or course of clinical care

Structural changes in the brain are associated with a range of diverse CNS symptoms[1]

Although structural changes are detectable in DM1 and associated with CNS symptoms, challenges in study design and reproducibility, and the lack of longitudinal and age-related data mean that the use of imaging as a tool for monitoring the progression of DM1 remains underdeveloped[2,3]

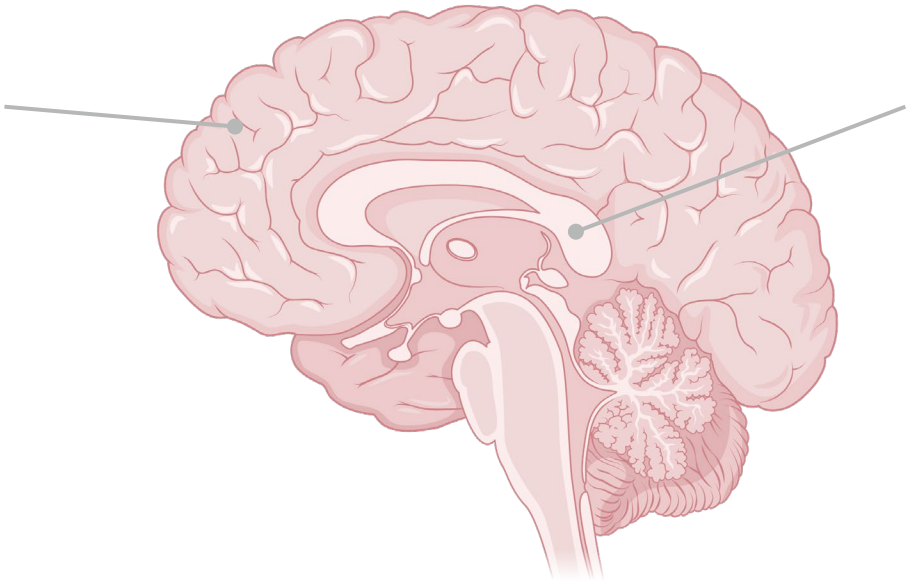
CNS, central nervous system; DM1, myotonic dystrophy type 1.

1. Meola G, et al. *Muscle Nerve*. 2007; 36(3):294–306; 2. Okkersen K, et al. *Neurology*. 2017;89(9):960–969; 3. Minnerop M, et al. *Front Neurol*. 2018;9:646.

Impaired cognition is associated with structural and functional brain abnormalities in DM1

Gray matter

- Gray matter atrophy is present in DM1[1–4]
- Gray matter atrophy is negatively associated with cognitive impairments*[2–4]
  - Recall[3]
  - Flexibility of thinking[2]
  - Visuoconstruction[4]
  - Executive performance[4]



White matter

- White matter volume and integrity is reduced in DM1[4,5]
- White matter abnormalities are associated with cognitive impairments*[1,7]
  - Working memory[1,7]
  - Reason and problem solving[1]
  - Visuospatial ability[1]

Hyperconnectivity

- Functional hyperconnectivity is detected and negatively correlated with cognitive performance[6]
  - Estimated IQ[6]
  - Visuoconstruction[6]
  - Executive function[6]

*List is not exhaustive.

DM1, myotonic dystrophy type 1; IQ, intelligence quotient. Image from BioRender.com.

1. Caso F, et al. *PLoS One*. 2014;9(8):e104697; 2. Schneider-Gold C, et al. *PLoS One*. 2015; 10(6):e0130352; 3. Jiang Q, et al. *Front Neurol*. 2022;13:891789; 4. Labayru G, et al. *Neuroimage Clin*. 2019;24:102078; 5. Labayru G, et al. *SciRep*. 2022;12:3988; 6. Garmendia J, et al. *J Neuromuscul Dis*. 2025;12(1):90–101; 7. Cabada T, et al. *Neuroradiology*. 2021;63(7):1019–1029.

Apathy is a behavioral and personality feature of DM1 that may have a central cause[1,2]

Apathy and white matter abnormality

Correlation with white matter abnormality (cerebral FA), N=39[3]

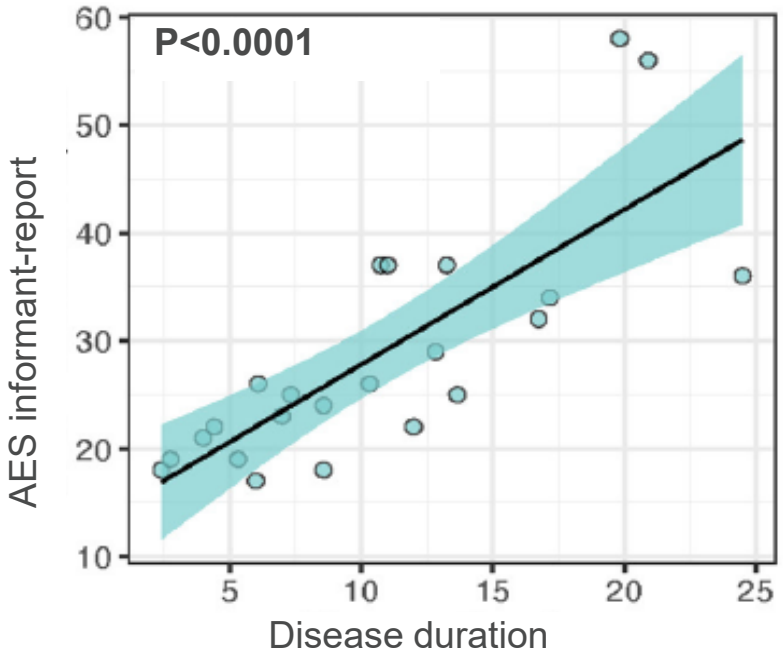
	t-value	R^2	P value
AES informant-report	−2.20	0.222	0.042

- Greater white matter abnormality was associated with higher informant-reported apathy scores[3]

"My son's apathy is his greatest challenge, along with making good choices. He even consciously doesn't take his methylphenidate when he wants to 'lay around all day.'"

Caregiver of adult with juvenile-onset DM1[4]

Apathy correlated with disease duration[3*]



Apathy was not correlated with fatigue, depression and state or trait anxiety and is not purely secondary to living with a chronic neuromuscular disease[2]

AES, Apathy Evaluation Scale; DM1, myotonic dystrophy type 1; FA, fractional anisotropy; LARS, Lille Apathy Rating Scale; MMSE, Mini Mental State Evaluation.

1. Simoncini C, et al. *Front Neurol*. 2020;11:624; 2. Gallais B, et al. *BMC Neurol*. 2015;15:148; 3. Miller JN, et al. *Front Neurol*. 2021;12:700796; 4. White M. *Ther Innov Regul Sci*. 2020;54(5):1010–1017.

Emotion and social cognition are influenced by brain changes

Depression scores and white matter brainstem volume

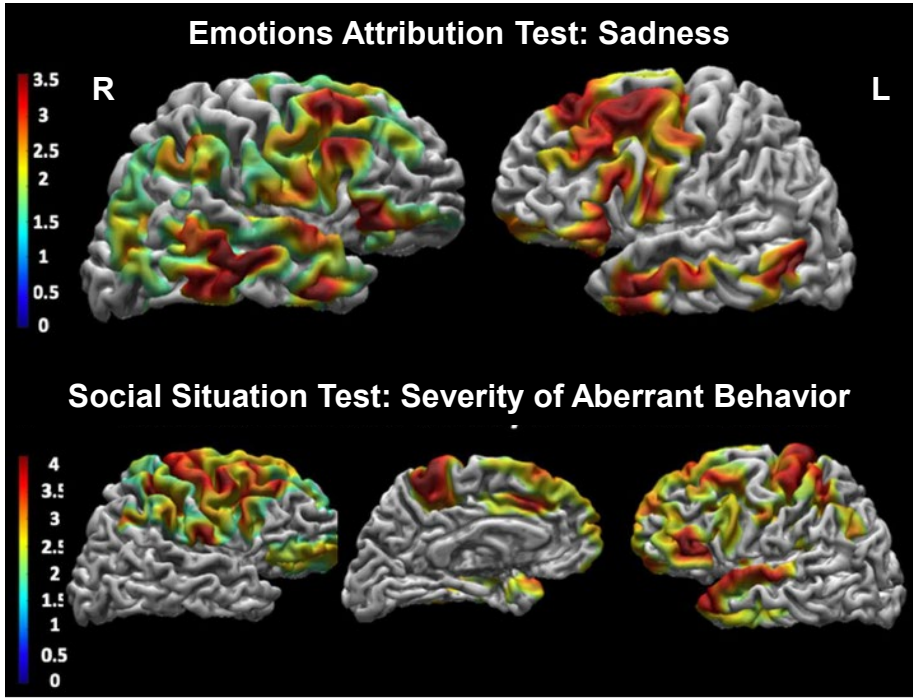
- A study of 12 individuals living with DM1[1]
  - Trend towards **white matter brainstem atrophy** in specific areas and **depression score**

CNS changes play a role in depression,[1] which is not only secondary to living with chronic illness

Social cognition performances and cortical thickness

- A study of 30 individuals living with DM1[2]
  - Significant decrease in **cortical thickness** in several brain areas
  - Correlations of CTG peripheral triplet expansion size with cortical abnormalities in specific brain areas
  - **Widespread impairment** of social cognition, involving emotion attribution, social situation, and moral judgment

Correlations between cortical thickness and performances in the social cognition battery test (redder color indicates increased correlation)[2]*



MRI brain scan overlain with statistical comparisons

Changes observed in areas known to play a key role in higher level functions and in areas important to mentalizing ability and empathy[2]

CNS, central nervous system; DM1, myotonic dystrophy type 1; L, left; MRI, magnetic resonance imaging; R, right.

1. Schneider-Gold C, et al. *PLoS One*. 2015;10(6):e0130352; 2. Serra L, et al. *Front Neurol*. 2020;11:113.

Fatigue in DM1 has distinct etiologies and is influenced by brain changes

CNS-driven

Central fatigue due to brain changes that reduces voluntary muscle activation[1]

Muscle-driven

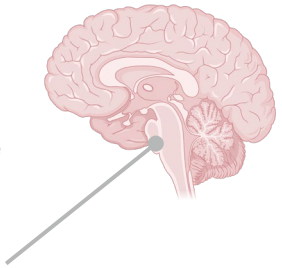
Peripheral fatigue due to atrophy of muscle fibers[1]

- A study of 64 individuals living with DM1[2]
  - Worsening of fatigue was independent of muscle weakness progression over 7-year follow-up
  - Change in fatigue was not correlated with change in muscle weakness

Fatigue, sleep, and brain changes

Brain structure changes

- Changes in specific areas of the brain have been linked to fatigue
  - Hippocampus volume has been positively correlated with self-reported fatigue in patients living with DM1 (n=36)[3]
  - Patients with fatigue were more likely to have altered tissue density in the raphe of the brainstem (n=102)[4]

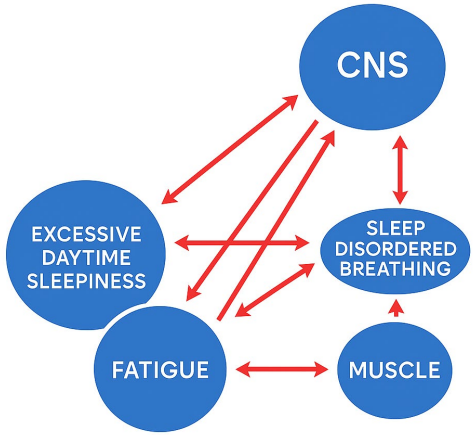


Brainstem raphe density is thought to reflect dysfunction of the brainstem reticular activating system (involved in arousal and attention)[5]

Sleep dysregulation

- Sleep architecture is altered in individuals with DM1, and associated with structural brain changes[3]

There is a complex interaction between factors that drive CNS symptoms in DM1[6]



Fatigue can be overlooked as secondary to muscular symptoms,[2] but CNS-driven fatigue plays a key role[1]

CNS, central nervous system; DM1, myotonic dystrophy type 1.

Brain image from BioRender.com. Sleep dysregulation figure used with permission of Wiley, from Subramony SH, et al. *Muscle Nerve*. 2020;62(3):309–320, permission conveyed through Copyright Clearance Center, Inc.
1. Angelini C, et al. *Neuromuscul Disord*. 2012;22 Suppl 3(3-3):S214–S220; 2. Peric S, et al. *Acta Myol*. 2019;38(4):239–244; 3. Hamilton MJ, et al. *Neuromuscul Disord*. 2022;32(5):377–389;
4. Mijajlovic M, et al. *Heliyon*. 2024;10(5):e26856; 5. Arguinchona JH, Tadi P. Neuroanatomy, Reticular Activating System. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL). StatPearls Publishing; 2026 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549835/; 6. Subramony SH, et al. *Muscle Nerve*. 2020;62(3):309–320.

Excessive daytime sleepiness in DM1 is likely related to abnormalities of sleep regulation structures in the brain

CNS-driven

Alterations in **sleep structure** (phases of sleep) due to changes in **brain structure** and **sleep disordered breathing** due to impaired central respiratory drive[1]

Muscle-driven

Obstructive sleep apnea due to craniofacial changes and sleep disordered breathing arising from respiratory muscle impairment[1]

Excessive daytime sleepiness, sleep, and brain changes

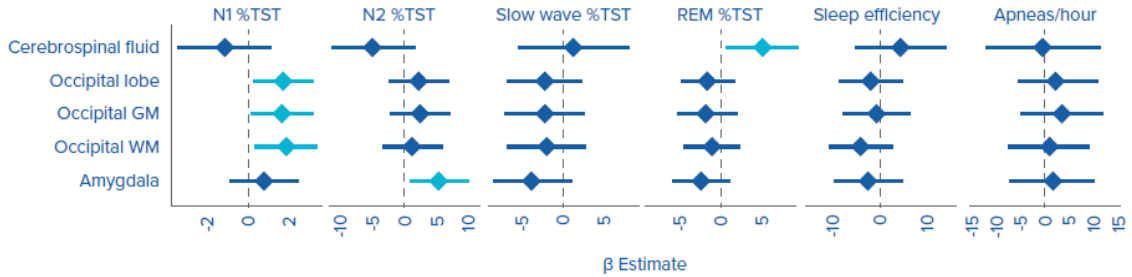
Brain structure changes

- Volume changes in specific areas of the brain have been linked to excessive daytime sleepiness[2,3]

Sleep dysregulation

- Circadian rhythm sleep disorders may be more common in DM1[4]
- Actigraphy shows poorer sleep quality and delayed sleep–wake episodes compared with healthy controls[4]
- Multiple sleep studies have reported the presence of a “narcolepsy-like” phenotype in individuals with DM1[5]
- Individuals with DM1 show increased proportions of slow-wave and REM sleep, and dysregulation of REM sleep[3,5]
- Reduced density of serotonergic neurons – considered to be involved in sleep regulation – has been observed in the individuals with myotonic dystrophy, supporting a direct CNS impact on sleep[6]

Select relationships between regional brain volumes and sleep measures[3]



Statistically significant relationships (light blue bars; p<0.05)

Non-invasive ventilation such as CPAP has shown limited efficacy in DM1,[7,8] which further supports the role of the CNS in sleep-disordered breathing

Available evidence suggests that the CNS is the primary driver of DM1-related excessive daytime sleepiness[9]

CNS, central nervous system; CPAP, continuous positive airway pressure; DM1, myotonic dystrophy type 1; REM, rapid eye movement. Image adapted from Hamilton MJ, et al. *Neuromuscul Disord*. 2022;32(5):377–389, licensed under a CC-BY 4.0 Creative Commons license; doi: doi: 10.1016/j.nmd.2022.02.003.

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Summary

DM1 is a multi-systemic disease

- DM1 is a multi-systemic disease that presents with muscular and non-muscular symptoms and features
- CNS involvement in DM1 is common yet heterogeneous
- Although CNS manifestations vary by DM1 clinical phenotype and age of onset, almost every individual experiences some form of CNS involvement

CNS involvement in DM1 is driven by spliceopathy

- CNS involvement is driven by a spliceopathy caused by the sequestration of MBNL splicing factors into mutant nuclear RNA structures that result from expansions of an unstable CTG repeat in the *DMPK* gene
- Spliceopathy has been demonstrated within the CNS and linked to genes implicated in CNS pathology

CNS changes in DM1 have a broad impact

- Changes within the CNS contribute to symptoms in individuals living with DM1, including alterations in cognition, behavior/personality, emotion, fatigue, excessive daytime sleepiness, and sleep dysregulation

ASO, antisense oligonucleotide; CNS, central nervous system; CTG, cytidine–thymidine–guanosine; DM1, myotonic dystrophy type 1; *DMPK*, dystrophia myotonica protein kinase; MBNL, muscleblind-like; RNA, ribonucleic acid; TfR1, humanized transferrin receptor 1.