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ε-sarcoglycan myoclonus-dystonia—overview of neurophysiological, behavioral, and imaging characteristics

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Myoclonus-Dystonia is a rare, neurological movement disorder, clinically characterized by myoclonic jerks and dystonic symptoms, such as cervical dystonia and writer's cramp. Psychiatric symptoms, like anxiety, depression, and addiction, are frequently reported. Monogenic Myoclonus-Dystonia is mostly caused by pathogenic variants in the *ε-sarcoglycan* gene, which is among other regions highly expressed in the cerebellum. The current pharmacological treatment is not satisfactory. Neurophysiological and imaging studies in this patient population are scarce with partly heterogeneous results and sometimes important limitations. However, some studies point towards subcortical alterations, e.g., of the cerebellum and its connections. Further studies addressing previous limitations are important for a better understanding of the underlying pathology of Myoclonus-Dystonia and might build a bridge for the development of future treatment.

KEYWORDS

dystonia, cerebellum, neurophysiology, SGCE, myoclonus

Introduction

Myoclonus-Dystonia (M-D) is a rare, childhood-onset movement disorder characterized by myoclonic jerks predominantly in the upper body, and dystonia, mostly cervical dystonia and writer's cramp [1–4]. Motor symptoms are often alcohol responsive [5]. M-D is often associated with psychiatric symptoms, such as anxiety [6–13], obsessive compulsive disorders [8–10, 14–18], depression [6, 7, 9–13], and alcohol abuse/dependence [1, 8, 9, 13–18], which can also be present in unaffected mutation carriers [8, 17].

The most frequent cause of M-D are pathogenic variants (mostly loss-of-function) in the *ε-sarcoglycan* gene (*SGCE*) (OMIM #159900, DYT11) [15, 19–21]. *SGCE*-positive M-D is inherited in an autosomal-dominant manner with maternal imprinting, resulting in reduced penetrance [22, 23]. Thus, ~95% of *SGCE* mutation carriers, whose variant is

maternally inherited, are unaffected, but nearly all mutation carriers, who inherit their variant paternally, develop symptoms [24].

SGCE is widely expressed in the brain, but different isoforms of *SGCE* appear in a differential expression pattern [25]. The brain-specific isoform is highly expressed in the cerebellum [25].

Unfortunately, pharmacological treatment of M-D is mostly not satisfactory [26, 27] and/or has intolerable side effects [27, 28].

An important treatment option is deep brain stimulation (DBS) of the globus pallidus internus (GPi) and the thalamus (ventral intermediate nucleus, VIM), which can significantly improve myoclonus and dystonia [28–37]. However, several patients are not eligible for DBS or are too afraid of the side effects [33].

This lack of fully satisfactory and causally effective treatment options highlights the need for further research to better understand underlying disease mechanisms.

Neurophysiological, behavioral, and imaging studies in these patient population are scarce. It has been proposed, that *SGCE*-positive M-D is a network disorder with the cerebellum and its connections as an important hub [38]. The following is an overview of the state of research on subcortical alterations in M-D. It illustrates limitations but also potentials to foster future research strategies and therapeutical implications, that might result from them. The term M-D describes *SGCE*-positive M-D in the following, deviations are explicitly stated. Further details on the described studies investigating patients with M-D can be found in Table 1.

Subcortical alterations in myoclonus-dystonia

Myoclonus in general can have a cortical or a subcortical origin and thus present with different neurophysiological characteristics [61]. With regards to M-D, the duration of the myoclonic bursts (mean duration 95 msec) indicated a subcortical origin [2], as cortical myoclonus is described with shorter durations between 20 and 50 msec [2]. The hypothesis of a subcortical origin is supported by a lack of cortical hyperexcitability, e.g., absence of giant somatosensory evoked potentials (SEPs) [49, 50]. Although, in some patients with M-D myoclonic jerks can be evoked by certain stimuli (e.g., visual, auditory, sensory) [49, 50], which could be interpreted as a sign of a cortical source [62], the stimulus-evoked jerk latency in M-D was consistent with a subcortical origin [50].

Basal ganglia alterations in myoclonus-dystonia

Subcortical alterations were also found with structural and functional imaging techniques. Voxel based morphometry (VBM) studies showed no significant differences in white or gray matter of the basal ganglia in M-D patients, but increased severities of dystonia [42] and myoclonus [59] were associated with larger putaminal volumes. Functional imaging with [^{18}F]-fluorodeoxyglucose binding revealed genotype related alterations of subcortical metabolic activity in M-D patients and asymptomatic *SGCE*-positive mutation carriers [43]. Metabolic increases in pontine and thalamic brain areas were present in all *SGCE* mutation carriers compared to healthy controls [43].

The hypothesis of a subcortical deficit in M-D is also supported by treatment effects in M-D, particularly DBS of the GPi or the VIM [38], and also by altered activity of GPi neurons [47, 54].

In patients with dystonia, it is thought that the direct motor pathway via striatal D1 receptors is hyperactive, which might result in a reduced GPi activity, and therefore, a disinhibition of the thalamus, and an increased thalamocortical output [63]. On the other hand, it is suggested that the activity of the indirect motor pathway via striatal D2 receptors is reduced in patients with dystonia [63]. This explanatory framework might also fit for the hyperkinetic symptoms, e.g., dystonia and myoclonus, present in M-D.

In this regard, an interesting strategy to investigate the hubs of the direct and indirect motor pathways is the use of intracranial DBS electrodes, either intraoperative during DBS implantation surgery or shortly after the operation when the impulse generator is not connected yet and electrodes are externalized. A coherence analysis investigating the synchrony (i.e., correlation) between muscle discharges, recorded with electromyography (EMG), and (motor associated) neural activity, recorded by local field potentials (LFP) of the basal ganglia via DBS electrodes, or cortical activity recorded by electroencephalography (EEG) [64], is very helpful to draw further conclusions how movements are controlled or influenced by (sub-)cortical activity [65]. Increased cortico-muscular coherence (3–15 Hz) between several muscles and the GPi-LFP during rest and voluntary muscle activation was identified in M-D patients after GPi-DBS surgery and could reflect abnormal, e.g., increased GPi activity [47]. In another study, GPi recordings revealed a higher burst activity, which correlated with a higher preoperative severity of myoclonus in M-D patients in comparison to generalized dystonia patients, and thus seems to be specific for the myoclonus phenotype [54].

The hypothesis, that hypoactivation of the indirect pathway might contribute to the pathogenesis of M-D, is supported by findings of reduced striatal [^{123}I]-Iodobenzamide binding, reflecting lower dopamine D2 receptor binding [39]. After treatment with GPi-DBS for 2 years, striatal dopamine D2 receptor binding did not decrease further, as it was the case in M-D patients without GPi-DBS, suggesting a stabilization on dopamine pathways due to GPi-DBS [30].

Defective basal ganglia mediated motor inhibition, investigated with a “Go/NoGo” task, where it is required to react to a “Go” cue and to suppress a reaction to a “NoGo” cue, has been found in a group of *SGCE*-positive and *SGCE*-negative

TABLE 1 Overview of neurophysiological, imaging, and behavioral/psychophysical studies investigating patients with Myoclonus-Dystonia.

Reference number in the article	Sample characteristic	Control group characteristic	Research method	Experimental tasks	Results
Imaging studies					
[39]	15 *SGCE*-MC (11 pat., 4 AMC)	15 age- and sex-matched HC	[^{123}I]-IBZM SPECT	n.a.	Bilateral lower striatal D2R binding in M-D pat. and AMC compared to HC
[40]	13 M-D pat.	11 age-, and sex-matched HC	fMRI	Finger-tapping task	Hyperresponsiveness in contralateral inferior parietal cortical areas, ipsilateral premotor and primary somatosensory cortex, and the ipsilateral cerebellum in M-D pat. compared to HC
[41]	16 *SGCE*-MC (8 pat./ paternally inherited, 8 AMC/maternally inherited)	11 HC	fMRI	Finger-tapping task	Hyperresponsiveness in the contralateral secondary somatosensory cortex in M-D pat. compared to AMC
					Hyperresponsiveness in the supplementary motor area and the ipsilateral cerebellum in AMC compared to HC
[42]	25 M-D pat.	25 age-, and gender-matched HC	Structural MRI (VBM)	n.a.	No significant differences in gray and white matter volumes between M-D pat. and HC
					In M-D pat., positive correlation of dystonia severity with increased gray matter volume in bilateral putamina
[30]	3 M-D pat. with GPi-DBS (examined before and approx. 2 years after GPi-DBS implantation)	2 M-D pat. without GPi-DBS (examined twice, approx. 3.5 years apart)	[^{123}I]-IBZM SPECT	n.a.	D2R binding was stable in M-D pat. with GPi-DBS after 2 years, but reduced in M-D pat. without GPi-DBS after 3.5 years
[43]	12 *SGCE*-MC (6 pat., 6 AMC)	24 HC, 18 DYT1/*TOR1A* pat., 13 DYT6/*THAP1* pat., 9 dopa-responsive dystonia pat., 7 posthypoxic myoclonus pat.	[^{18}F]-FDG-PET	n.a.	Metabolic increases in the inferior pons and in the posterior thalamus and reductions in the ventromedial prefrontal cortex in all *SGCE*-MC compared to HC
					Metabolic increases in the parasagittal cerebellum in M-D pat. compared to AMC and HC
					M-D pat. shared metabolic increases in the parasagittal cerebellum with pat. with posthypoxic myoclonus
					M-D pat. shared significant metabolic increases in the superior parietal lobule with all dystonia pat. subgroups

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TABLE 1 (*Continued*) Overview of neurophysiological, imaging, and behavioral/psychophysical studies investigating patients with Myoclonus-Dystonia.

Reference number in the article	Sample characteristic	Control group characteristic	Research method	Experimental tasks	Results
					M-D pat. shared metabolic reductions with DYT1/*TOR1A* pat. in the ventromedial prefrontal cortex
[44]	1 M-D pat.	1 age-matched HC	fMRI	Motor task (drawing, snapping)	Specific activations within the thalamus and the dentate nucleus of the M-D pat. during the drawing condition with snapping as control, which was not present in the HC
[45]	16 M-D pat.	18 age-, and sex-matched HC	Structural MRI (white matter VBM, DTI)	n.a.	Increased white matter volume, fractional anisotropy and decreased mean diffusivity in the subthalamic area of the brain stem (including the red nucleus) in M-D pat. compared to HC. Decreased mean diffusivity in the subgyral cortical sensorimotor area in M-D pat. compared to HC
[46]	24 M-D pat. (15 *SGCE*-positive)	24 gender-, age-, education-, and handedness-matched HC	fMRI	Go/No-Go task	Impaired response accuracy in M-D pat. (frequent Go-Inhibit errors/incorrect response-inhibition to Go cues)
					Increased primary motor cortex and insular activation in M-D pat. compared to HC
					Increased activity in the contralateral thalamus and the dorsolateral prefrontal cortex in M-D pat. during Go-Inhibit trials
					SGCE-positive pat. showed on all contrasts (all possible response trials) hyperactivation in the anterior cerebellum and in the Stop-Respond trial (incorrect response to Stop cue) contrast increased putaminal activation compared to *SGCE*-negative pat.
Neurophysiological studies					
[47]	2 M-D pat. with GPi-DBS	n.a.	LFP, EMG	Motor task & Go/No-Go task	Increased EMG-GPi-LFP coherence in the 3–15 Hz frequency band in motor task

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TABLE 1 (*Continued*) Overview of neurophysiological, imaging, and behavioral/psychophysical studies investigating patients with Myoclonus-Dystonia.

Reference number in the article	Sample characteristic	Control group characteristic	Research method	Experimental tasks	Results
					During the Go/No-Go task, synchronization of GPi activity in the 3–15 Hz frequency band before the cue (Go or No-Go) and desynchronization after the cue
[48]	20 *SGCE*-MC (15 pat., 5 AMC)	13 approx. age-, and sex-matched (to the pat.) HC	EEG-EMG and EMG-EMG coherence	Rest and contraction of the arm and neck (and, if affected, of the trunk)	Significant 15–30 Hz EEG-EMG coherence during arm contraction in HC, but not in *SGCE*-MC
					Increased 3–10 Hz EMG-EMG coherence in M-D pat. with pronounced dystonia
[49]	6 M-D pat.	9 age-matched HC	EMG, EEG, TMS, median and digital nerve stimulation	JLBA, SEP, LLR, RMT, AMT, SICI (rest and active), ICF (rest and active), LICI (rest and active)	JLBA EEG showed no preceding cortical correlates of myoclonus
					Normal LLR to median or digital nerve stimulation, normal SEP, RMT, AMT, SICI, ICF, and LICI in M-D pat. compared to HC
[50]	9 M-D pat.	HC (not further specified)	EMG, EEG, TMS	SEP, VEP, LLR, ERS, ERD, JLBA, RMT, AMT, SICI, LICI, SP, SICF, blink reflex recovery	Normal SEP, VEP, ERD, LLR, SP, RMT, AMT, SICF, and LICI, subtle impairment in SICI, and delayed ERS in the beta band in M-D pat. compared to HC
					No EEG correlate of myoclonus revealed by JLBA EEG
					In M-D pat., strongly enhanced blink reflex recovery
[51]	5 *SGCE*-MC (4 pat., 1 AMC)	10 age-, and handedness-matched HC	TMS	AMT, SICI, AI, SICI- and AI-interaction	Higher AMT in *SGCE*-MC compared to HC
					No significant differences between *SGCE*-MC and HC in SICI, AI, and their interaction
[52]	12 M-D pat.	12 age-, and sex-matched HC	TMS, motor learning	(r)RMT, (r)AMT. SICI, SICF, RPAS, EBCC	Normal RMT and AMT in M-D pat. compared to HC using monophasic pulses
					Increased rAMT and borderline increased rRMT, i.e., not significant trend, in M-D pat. compared to HC using biphasic pulses
					Positive correlation of rAMT and rRMT with self-rated global disability score

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TABLE 1 (*Continued*) Overview of neurophysiological, imaging, and behavioral/psychophysical studies investigating patients with Myoclonus-Dystonia.

Reference number in the article	Sample characteristic	Control group characteristic	Research method	Experimental tasks	Results
					No differences in SICI and SICF in M-D pat. compared to HC
					RPAS effects lasted longer in M-D pat. compared to HC
					Lower extinction rates in the EBCC task in M-D pat. compared to HC
[2]	41 M-D pat.	n.a.	EEG, EMG	Surface polymyography, long-loop C-reflex, JLBA	M-D pat. showed subcortical myoclonus (mean duration 95 msec, range 25–256 msec) at rest, action, and posture, and no cortical hyperexcitability (normal C-reflex response, no short-latency premyoclonic potential)
[53]	15 M-D pat.	15 gender-, and age-matched HC	TMS	RMT, AMT, SP, RC, SICI, ICF, SICF, peripheral median nerve stimulation	Normal RMT, AMT, SP, RC, SICI, and ICF in M-D pat. compared to HC
					M-D pat. showed more variable and polyphasic MEPs during SICF
					No polyphasic compound muscle action potentials found in M-D pat. and HC with peripheral median nerve stimulation
[54]	6 M-D pat.	6 primary-generalized dystonia pat.	Microelectrode recording during GPi-DBS implantation surgery	n.a.	In M-D pat., higher burst frequency, with a higher burst index, a lower mean burst duration, and a lower interburst interval in GPi neurons, and higher pause frequency in GPe neurons compared with pat. with primary-generalized dystonia
					In M-D pat., significant correlation of GPi activity (mean burst index, burst duration, intraburst frequency and interval, pause and oscillatory frequency) with the preoperative severity of myoclonus
					In M-D pat., significant correlation of preoperative dystonia severity with GPi activity (mean burst duration and pause frequency)

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TABLE 1 (*Continued*) Overview of neurophysiological, imaging, and behavioral/psychophysical studies investigating patients with Myoclonus-Dystonia.

Reference number in the article	Sample characteristic	Control group characteristic	Research method	Experimental tasks	Results
					In primary-generalized dystonia pat., significant correlation of preoperative dystonia severity with GPi activity (mean intraburst frequency and interburst interval) and GPe activity (intraburst frequency)
Behavioral and psychophysical studies					
[55]	31 M-D pat. (12 with GPi-DBS, 21 without GPi-DBS)	24 matched HC	Behavioral Task	Stop signal task	Impaired proactive inhibition in M-D pat. without GPi-DBS (no adaptation to consecutive cues)
					Impaired reactive inhibition in M-D pat. with GPi-DBS (longer stop signal reaction times)
[56]	14 M-D pat.	14 age- and gender-matched HC	Eye-tracking	Backward saccadic adaptation	Saccadic adaptation was lower and slower in M-D pat. compared to HC
[57]	5 M-D pat.	10 age-matched HC	Limb adaptation	Limb adaptation to visuomotor and forcefield pertubation	No difference between M-D pat. and HC
[58]	23 M-D pat.	25 age-, gender-, and educational level-matched HC	Tactile sensory information processing	Tactile TDT, TT	No difference between M-D pat. and HC in TT threshold
					M-D pat. showed increased TDT compared to HC
[59]	37 M-D pat. (24 without GPi-DBS, 13 with GPi-DBS)	25 HC	Visual sensory information processing, structural MRI (VBM)	Visual TDT, orientation of random dot moving task, speed of random dot moving task, ODT, SDT	Higher TDT in M-D pat. with GPi-DBS, compared to HC and M-D pat. without GPi-DBS
					Reduced sensory accumulation for visual information in M-D pat. compared to HC in all tasks
					No differences in ODT and SDT in M-D pat. compared to HC
					Thicker primary visual cortex (which negatively correlated with TDT performance) and higher gray matter signal of left motor cerebellum (lobules V and VI) in M-D pat. (without GPi-DBS) compared to HC
					Negative correlation of myoclonus severity with TDT performance and

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TABLE 1 (*Continued*) Overview of neurophysiological, imaging, and behavioral/psychophysical studies investigating patients with Myoclonus-Dystonia.

Reference number in the article	Sample characteristic	Control group characteristic	Research method	Experimental tasks	Results
					positive correlation with left primary visual cortex and bilateral putaminal volumes in M-D pat. (without GPi-DBS)
[60]	17 M-D pat.	21 age- and sex-matched HC	Motor learning	EBCC, blink reflex recovery cycle	Significantly reduced number of conditioned eyeblink responses before alcohol intake in M-D pat. compared to HC
					In M-D pat., negative correlation of action myoclonus severity at baseline with EBCC conditioning response
					Decreased conditioning response rate under alcohol intake in HC
					In M-D pat., increased conditioning response rate under alcohol intake
					No group difference (M-D pat. vs. HC) in blink reflex recovery cycle before and after alcohol intake

Note. Studies are sorted in an alphabetical manner. M-D pat., *SGCE*-positive patients with Myoclonus-Dystonia; pat., patients; *SGCE*, *ε-sarcoglycan* gene; GPi, Globus Pallidus internus; DBS, deep-brain stimulation; (A)MC, (asymptomatic) *SGCE* mutation carrier; I-IBZM SPECT, [^{123}I]-Iodobenzamide single photon emission computed tomography; n. a., not applicable; D2R, dopamine D2 receptor; HC, healthy control participants; (f)MRI, (functional) magnetic resonance imaging; VBM, voxel based morphometry; DTI, diffusion tensor imaging; FDG-PET, [^{18}F]-fluorodeoxyglucose positron-emission tomography; LFP, local field potential; EMG, electromyography; EEG, electroencephalography; TMS, transcranial magnetic stimulation; JLBA, Jerk-locked back-averaging; SEP, somatosensory evoked potentials; VEP, visual evoked potentials; LLR, long-latency reflex; SICI, short-interval intracortical inhibition; (S)ICF, (short-interval) intracortical facilitation; LICI, long-interval intracortical inhibition; ERS, event-related synchronization; ERD, event-related desynchronization; MEP, motor evoked potential; RC, recruitment curve; SP, silent period; (r)AMT, (rapid/biphasic) active motor threshold; AI, afferent inhibition; (r)RMT, (rapid/biphasic) resting motor threshold, RPAS, rapid paired associative stimulation; EBCC, eye-blink classic conditioning; TDT, temporal discrimination threshold; TT, tactile perception threshold; ODT, orientation discrimination threshold; SDT, speed discrimination threshold; GPe, Globus Pallidus externus.

M-D patients, suggesting that these abnormalities might be related to phenotype rather than genotype [46].

The role of the basal ganglia, especially the GPi, during motor inhibition in M-D was further undermined using a "stop signal" task, which investigates reactive (stop an already started action) and proactive (action inhibition during action preparation) inhibition [55]. M-D patients with GPi-DBS showed impaired reactive inhibition and M-D patients without GPi-DBS exhibited impaired proactive inhibition [55]. The impairments in reactive inhibition correlated with the intrinsic/preoperative severity of myoclonus. This could indicate that GPi-DBS on the one hand improves proactive inhibition, but on the other hand impairs reactive inhibition. Moreover, response inhibition involves the hyper-direct and the direct pathway and potentially also the striato-nigral pathway, which is known to be modulated by GPi-DBS [55].

To sum up, results of neurophysiological, behavioral, and imaging studies, as well as treatment effects of DBS, point to a subcortical deficit in M-D. Especially a dysfunction of the basal ganglia circuits, including the GPi, might contribute to abnormal excitatory output and connectivity with other subcortical and cortical output regions.

Cerebellar alterations in myoclonus-dystonia

Besides the basal ganglia and its connections, there is emerging evidence that the cerebellum might be involved in the pathogenesis of M-D [40, 41–46, 56, 58, 60]. With regards to structural brain imaging, a VBM study revealed a higher gray matter signal in the left motor cerebellum (lobules V and

VI) in M-D patients compared to healthy control participants [59]. Furthermore, changes of white matter bilateral in subthalamic areas of the brain stem, connecting the cerebellum with the basal ganglia, were observed via VBM and diffusion tensor imaging (DTI) [45].

Increased metabolic activity in the parasagittal cerebellum has been found in M-D patients, but not in asymptomatic *SCGE*-positive mutation carriers and healthy controls [43]. Furthermore, these metabolic increases were also found in patients with posthypoxic myoclonus, which was interpreted as phenotype- (i.e., myoclonus) specific cerebellar metabolic abnormality [43].

In functional magnetic resonance imaging (fMRI) studies using different motor tasks, cerebellar regions were hyperactive in M-D patients [40, 44, 46], and asymptomatic *SGCE*-positive mutation carriers, who did not report symptoms by themselves, but had subtle signs of M-D in a detailed motor examination [41]. These cerebellar hyperactivations might be genotype-specific, as they also allowed separating asymptomatic *SGCE* mutation carriers from healthy controls [41], and *SGCE*-positive from *SGCE*-negative M-D patients [46].

Cerebellar function can also be assessed with the help of behavioral tasks, as the cerebellum contributes to non-declarative forms of learning, e.g., motor learning or classical conditioning [66]. Classical conditioning can be investigated in an experimental setting with an eyeblink conditioning task [67]. Thereby, the connection between an neutral conditioned stimulus (CS), usually a tone, and a response to be conditioned (conditioned response), a blink (e.g., triggered by an air puff or electrical stimulus) is learned and subsequently unlearned. It is thought, that eyeblink conditioning is mediated via brainstem-cerebellar connections, e.g., between pontine nuclei, the inferior olive, and the cerebellum [66]. Studies in patients with cerebellar lesions suggest a strong cerebellar involvement in the acquisition of the conditioned response [66]. Moreover, functional imaging of healthy participants showed activation in the cerebellar lobules VI, Crus I and II, VIIb, VIII, interposed nuclei, and dentate nuclei during acquisition of the conditioned response [68].

M-D patients showed decreased cerebellar motor learning, reflected by reduced acquisition of the conditioned response, and therefore, a poorer performance in the eyeblink conditioning task [60]. After consuming alcohol, myoclonus and the acquisition of the conditioned response improved in M-D patients, but decreased in healthy controls [60]. A proposed mechanism might be, that alcohol probably increases inhibitory GABAergic transmission and improves dysfunctional cerebellar disinhibition in M-D, but disrupts physiological cerebellar activity in the healthy brain [60]. This hypothesis of an "overactive", disinhibited cerebellum might be supported by the fMRI results of cerebellar hyperactivation during motor tasks as described above [40, 41, 44, 46].

Contrary to these findings, in another study, a smaller cohort of M-D patients showed normal eyeblink conditioning acquisition/learning rates, but lower extinction rates, i.e., difficulties in unlearning the conditioned response [52]. Methodological differences (air vs. electrical stimulation, trial numbers) and differences in sample size and characteristics should be kept in mind, when interpreting and comparing results [52, 60].

Other blink reflex measurements such as the blink reflex recovery cycle, which analyzes brain stem-basal ganglia interactions, showed a greater/faster mean recovery [50]. However, in a larger group of M-D patients, the blink reflex recovery cycle was normal, suggesting normal brain stem-basal ganglia interactions [60], and a more pronounced cerebellar deficit in M-D [60].

Another technique to assess cerebellar motor learning is saccadic adaptation [56]. Adaptation in general requires learning of an artificially induced movement error [69]. In the case of saccadic adaptation, a visual target is moved after movement initiation, so a corrective eye movement, i.e., a saccade, must be learned [69]. In a backward reactive saccade adaptation task, which involves the cerebellar vermis (lobules VI and VII), M-D patients showed slower saccadic adaptation [56]. Interestingly, impairment in a saccadic adaptation task can also be observed in healthy participants following inhibitory repetitive transcranial magnetic stimulation (rTMS) of the posterior vermis [70]. This suggests reduced function of the posterior vermis in M-D patients, which is also consistent with the observed metabolic differences along the parasagittal cerebellum in M-D patients as described above [43].

To test, if potential deficits in cerebellar adaptation function might also affect limb adaptation, visuomotor or forcefield perturbation in symptomatic body parts was examined [57]. In comparison to the deficits in saccadic adaptation [56], no differences were found in other tasks, suggesting that deficits in saccadic adaptation are not easily translatable to other body regions. However, potential deficits in limb adaptation might be more subtle and need to be investigated in larger sample sizes, as the current study only included five patients [57]. Also, methodological differences, and the potential contribution of different brain regions have to be kept in mind [57].

The association between the cerebellum and motor learning deficits in M-D is also supported by results from a paternally-inherited cerebellar Purkinje cell-specific *Sgce* conditional knockout mouse model [71]. These mice showed motor learning deficits, whereby, paternally-inherited *Sgce* heterozygous (non-conditional) knockout mice showed additional myoclonus, psychiatric alterations (depression- and anxiety-like behaviors), and motor impairments [72]. This might be an indication, that an impairment of motor learning is mostly influenced by a loss of function of cerebellar *SGCE*, whereas defective *SGCE* in other brain regions might contribute to the development of other symptoms of M-D, like myoclonus [71, 72].

In conclusion, although the cerebellum (and its connections to other brain areas) is recognized as a region of particular interest in M-D, its contribution to M-D symptoms remains largely unclear. Imaging data showed that the cerebellum is a promising region to discriminate between *SGCE*-positive mutation carriers and healthy controls, and *SGCE*-positive and *SGCE*-negative M-D patients. In addition, behavioral tasks such as eye-blink conditioning and saccadic adaptation are an important research strategy as they are less prone to motion artefacts than imaging data and can be used in patients who are not suitable for MRI.

Subcortical-cortical network alterations in myoclonus-dystonia

There is emerging evidence, that dystonias are sensorimotor disorders, as evidences, for instance, by sensory phenomena including symptom improvement by sensory tricks [73], or increased temporal discrimination thresholds, even in unaffected relatives of patients [74]. The cerebellum itself is involved in somatosensory processing, as it receives somatosensory input via the spinal cord, visual and auditory systems, and trigeminal nuclei [75, 76]. It monitors and adjusts executed movements by comparing planned movements (efference copy) and somatosensory feedback [76]. Thus, sensory deficits found in M-D might be influenced by cerebellar and basal ganglia dysfunction in M-D.

In this regard, in addition to motor learning and motor inhibition difficulties, M-D patients have also shown sensory abnormalities in the visual and tactile domain [58, 59].

Visual sensory processing seems to be impaired in M-D patients with GPi-DBS, who had higher visual temporal discrimination thresholds than M-D patients without GPi-DBS and healthy control participants [59]. Sensory accumulation, which is a computational analysis of the response times connected to the gain of visual sensory information, was lower in the whole M-D patient group compared to healthy controls in the visual temporal discrimination task, and also in a movement orientation and a movement speed discrimination task [59]. Patients with more severe myoclonus showed lower sensory accumulation in the visual temporal discrimination task, and had a thicker primary visual cortex. Because the deficits in visual sensory processing were correlated with the thickness of the primary visual cortex, a brain area elementary responsible for visual perception, the authors interpreted these abnormalities as a primary part of M-D, and not as a secondary phenomenon [59]. Moreover, the role of tactile sensory processing in M-D is underscored by another study, which showed increased tactile temporal discrimination thresholds with preserved tactile perception thresholds in these patients [58].

Furthermore, besides cerebellar hyperactivation during motor tasks (as described above), hyperactivation of the somatosensory cortex was found in M-D patients [40, 41], and further separated them from asymptomatic *SGCE* mutation carriers [41].

Moreover, the cerebellum is also connected with the motor cortex via dentato-thalamo-cortical pathways that are predominantly facilitatory, whereas connections between cerebellar Purkinje cells and the dentate nucleus are inhibitory [77].

Abnormal cerebellar activity could potentially influence the motor cortex, which could result in defective motor cortex and corticospinal excitability.

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, is suitable to investigate cerebellar-primary motor cortex connections. The majority of studies analyzed motor cortex excitability by measuring resting or active motor thresholds [49–53], or intracortical inhibitory processes [49–53].

Measures at rest were normal in M-D across studies, e.g., resting motor threshold [52] and recruitment curve of motor evoked potentials [53]. Measures with muscular preactivation, e.g., active motor threshold, were normal [52, 53], or, in contrast, increased [51, 52]. Myoclonic symptoms, as a part of M-D, appear more frequently during action compared to rest [38]. The increased active motor thresholds, reflecting a reduced excitability of the axon membranes during muscle activation [52], might show, that the deficit in M-D is action-specific. In the context of the hypothesis of abnormal cerebellar hyperactivation, increased active motor thresholds could reflect increased Purkinje cell inhibition on the deep cerebellar nuclei, and therefore, an enhanced inhibition of the motor cortex [76], reflected by increased active motor thresholds. On the other hand, if human M-D is associated with a dysfunction, e.g., decreased activity, of cerebellar Purkinje cells, it might also reduce the inhibition of the dentate nucleus, and therefore, increase the faciliatory cerebellar-thalamo-cortical loop and its excitatory output on the motor cortex. Although this would fit with the hypothesis of cerebellar hyperactivation and the hyperkinetic symptoms of M-D, i.e., myoclonic jerks and dystonia, it does not explain increased active motor thresholds. However, contradictory findings might also be explained with methodological differences, as, e.g., the increased active motor thresholds have only been found using biphasic TMS pulses in one study [52]. Additionally, motor thresholds might not be sensitive enough to reveal potential (subtle) network deficits [78].

The majority of other TMS protocols investigating short-interval intracortical inhibition [49, 51–53] and (short-interval) intracortical facilitation [49, 52, 53] were normal in different groups of M-D patients, suggesting intact cortical $GABA_A$ergic inhibitory and glutaminergic excitatory networks in M-D [49, 79, 80]. In addition, $GABA_B$ergic inhibitory networks during action and rest [81–83], investigated with silent periods [50, 53] and long-interval intracortical inhibition [49, 50], seem to be normal in M-D patients as well.

The above described method of coherence, referring to EMG-LFP investigations [47], can also be non-invasively applied with

either the combination of EMG and EEG (to analyze cortico-muscular coherence) or of two EMG channels (to analyze intermuscular coherence), if, e.g., the application of an EEG is not possible due to data contamination because of muscle artifacts [64]. The investigations of EEG-EMG and EMG-EMG coherence can give insights into potentially altered (sub-) cortical neuronal activity, as different oscillations have different neuronal generators, e.g., the olivo-cerebellar system with frequencies between 6–12 Hz, and the primary motor cortex with frequencies between 15–30 Hz and 30–60 Hz [64].

In a group of M-D patients and non-affected *SGCE* mutation carriers, physiological EEG-EMG coherence in the 15–30 Hz frequency band was absent during muscular contractions [48]. This altered cortical activity may be influenced by subcortical dysfunction [48]. Furthermore, phenotype-specific alterations of intramuscular coherence, i.e., a significantly increased EMG-EMG coherence (3–10 Hz), were present in M-D patients with pronounced dystonia, but not in those with mild dystonia and/or predominating myoclonus [48]. This might indicate altered subcortical activity, as increased EMG-GPi-LFP coherence was found in M-D patients as well (as previously reported), suggesting abnormal GPi activity [47]. With regards to the hypothesis of cerebellar hyperactivation in M-D, the increased coherence might also be influenced by altered olivo-cerebellar oscillations, because these occur at a similar frequency as those associated with increased coherence in M-D [64].

Overall, M-D patients show sensory dysfunction, reflected by altered visual and tactile processing on a behavioral level, and structural and functional imaging abnormalities. TMS results point towards an action-specific network deficit. Cortical $GABA_A$- and $GABA_B$ergic inhibitory networks, and excitatory glutaminergic networks seem to be unaffected in M-D. Abnormal cortico- and intermuscular coherence in M-D might be a consequence of altered subcortical activity.

Discussion of the reviewed literature and future perspectives

Behavioral, neurophysiological, and imaging studies in patients with M-D are scarce, used different modalities/protocols, and, thus, revealed partially heterogeneous results. Nevertheless, several studies point towards subcortical abnormalities, e.g., alterations of the cerebellum, the basal ganglia and their connections. However, so far, it remains unclear whether the described abnormalities are causal influencing other brain areas, e.g., the sensorimotor cortex, via cerebello-basal ganglia-thalamo-cortical connections, or whether the findings are a consequence of myoclonus and dystonia.

The cerebellum is linked with the basal ganglia, e.g., the cerebellar cortex is connected with the STN, and the dentate nucleus is directly connected with the substantia nigra and the GPi [84]. Thus, abnormal cerebellar activity might have a direct influence on the basal ganglia and *vice versa* [84]. Results from studies in non-human primates and rodents provide support, that cerebellar output mainly targets the indirect pathway of the basal ganglia [85]. Injection of rabies virus into the putamen and external segment of the globus pallidus (GPe) of macaques revealed a disynaptic connection between the output of the dentate nucleus and the striatum, and a trisynaptic connection with the GPe likely via intralaminar nuclei and/or the ventroanterior/-lateral thalamus [86]. Therefore, basal ganglia abnormalities in M-D might be influenced by abnormal cerebellar activity or *vice versa*.

To answer the question, if (cerebellar) alterations are a phenotype- or genotype-specific consequence, it is important to include asymptomatic *SGCE* mutation carriers and/or patients with myoclonus and/or dystonic features without *SGCE* mutations. This has been done previously in a few studies, however, the sample sizes were rather small and direct comparisons of the different groups were mostly missing, complicating statistical evaluation and interpretability of the results. One imaging study compared patients with M-D with other patient groups, e.g., with different genetic forms of dystonia, posthypoxic myoclonus, and also with asymptomatic *SGCE* mutation carriers [43]. The identified shared or delineating metabolic abnormalities are a meaningful example to define phenotype- or genotype-associated characteristics of M-D, e.g., myoclonus-associated increases in the parasagittal cerebellum, which were found in *SGCE*-positive M-D patients and not in asymptomatic *SGCE* mutation carriers on the one hand, and were shared with patients with posthypoxic myoclonus on the other hand [43]. Comparisons to other cerebellar disorders such as ataxia, cerebellar stroke, and essential tremor would be interesting to better understand potential cerebellar deficits in M-D. Moreover, it would be interesting to compare patients with the M-D phenotype but other monogenic causes, i.e., different pathogenic variants in *SGCE, VPS16, KCTD17*, and others genes [20], to further analyze phenotype- and genotype-associated mechanisms.

With regards to the clinical characterization of affected patients, it would be preferable to use video rating by movement disorders specialists, who are blinded with regards to genetic status, disease group, and treatment. This could be supplemented by sensor-based technology [87, 88], such as accelerometry or electromyography, and also video-based technology with infra-red cameras or subsequent video evaluation with artificial intelligence [89], to render clinical assessment more objective and to potentially identify more subtle abnormalities, e.g., in asymptomatic mutation carriers, or of symptom characteristics that cannot be assessed reliably on clinical grounds alone, e.g., the duration of myoclonic jerks.

Results of imaging studies partly revealed conflicting results, as some studies found, e.g., differences in gray and/or white matter, whereas others did not. One explanation might be heterogenous phenotypic presentation of M-D given that patients with the same

mutation can have different symptoms. Even in the absence of structural abnormalities in M-D patients compared to healthy controls, correlations between symptom severity and putaminal volume have been reported [42]. Such correlations might be more sensitive markers of phenotype-specific alterations than volume *per se*. Another explanation might be, that especially with imaging techniques, severely affected M-D patients, e.g., those with severe cervical or mobile dystonia, and/or severe myoclonus, are difficult to examine. Subclinical alterations of neural volume in less affected patients, which might be associated with M-D, but were still normal (i.e., not significantly different) compared to healthy controls, might reach significance through correlation analysis with clinical data, and the inclusion of more severely affected patients.

However, especially when arguing for larger M-D cohorts including patients with more severe phenotypes, the technical difficulties, i.e., artifacts in the data collection, due to the hyperkinetic motor symptoms and psychiatric comorbidities such as anxiety disorders, which can additionally hinder data collection, have to be considered when interpreting study results.

Small sample sizes, as seen in most M-D studies, are usually accompanied with low statistical power of results, which reduces the likelihood that a statistically significant effect is a "true" effect and *vice versa* [90]. Also, if an underpowered study finds a true effect, it is likely that the size of the effect is exaggerated, which has been referred to as "effect inflation" or "the winners curse" [90]. This can effect replication studies, which calculate their sample sizes with the inflated effect size and then find smaller effects, which are closer to the true effect sizes [90]. Effect inflation might also have happened in the reviewed literature, as effects found in studies with smaller sample sizes could not be replicated in studies with larger sample sizes and *vice versa*, e.g., studies investigating the blink-reflex recovery cycle and saccadic- and limb-adaptation [50, 56, 57, 60].

Moreover, effects of certain pharmacological drugs and alcohol on symptoms and brain excitability/connectivity alterations have not sufficiently been examined in M-D. Except for one study investigating the clinical and neurophysiologic effects of alcohol in M-D [60], there are no studies looking at the efficacy of pharmacological therapies in modulating neurophysiological or imaging characteristics. However, M-D patients with GPi-DBS have been examined neurophysiologically and compared to patients without GPi-DBS [30, 55, 59]. Longitudinal comparisons of patients pre and post DBS with longer follow-up periods after implantation are desirable, as described, for example, in the study investigating striatal D2 receptor binding [30]. Moreover, research on patients during implantation and/or with externalized electrodes can provide further insights in the activity of subcortical hubs of the motor network and also of direct DBS effects. However, the additional load and risks for patients have to be kept in mind.

Most M-D studies were unimodal, i.e., used only one technique, e.g., either imaging, behavioral, or one particular neurophysiological paradigm. Studies with multimodal approaches are largely missing, but could be helpful to obtain further clinical/behavioral-neurophysiological/imaging-genotypic correlations.

Identifying abnormal neuronal, e.g., cerebellar/basal ganglia activity either as being causal or as a consequence of symptoms in M-D, does not only give us a chance to further understand the pathophysiology of M-D but also to identify potential targets for non-invasive neuromodulation techniques, e.g., for M-D patients who are not eligible for DBS. Neuromodulation techniques make use of inducing neuronal plasticity, and therefore, modifying neuronal activity via, e.g., rTMS or transcranial electrical stimulation [91]. In different groups of patients with dystonia, neuronal plasticity seems to be increased [91].

In this regard, non-invasive brain stimulation techniques can be used to influence the excitability of brain regions such as the VIM, the GPi, or the cerebellum. As the VIM and the GPi are hard to reach by non-invasive stimulation, transcranial focused ultrasound protocols, either as an ablation or as a neuromodulation method, might be an interesting alternative [92]. A recently published study, examining patients with tremor-dominant Parkinson's disease or essential tremor, showed that high-intensity MRI-guided focused ultrasound ablation of the VIM reduced tremor and was also associated with functional reorganization of specific cerebellar regions, and therefore, alterations of the cerebello-thalamo-cortical network [93]. With regards to more superficial brain regions like the posterior cerebellum, also transcranial electrical and magnetic stimulation devices could be used to alter cerebellar excitability and thus influence cerebellar output [94–96]. Transcranial electrical stimulation, which can be fixed to the participants head, can be a reasonable alternative to stimulate hyperkinetic patients such as M-D. Different cerebellar stimulation techniques have been extensively evaluated in healthy participants, with cerebellar transcranial alternating current stimulation appearing to be the most robust method to alter cerebellar activity [94–96] and are currently investigated in M-D.

In summary, cerebellar-basal ganglia-thalamo-cortical networks seem defective in M-D. However, some major questions are still unanswered and justify further research efforts. Till now, it is unclear whether the cerebellum is the major generator causing symptoms, or affected secondarily with other major players causing symptoms. Moreover, it is unsolved whether the neurophysiological and imaging alterations are the cause or the consequence of the phenotype and how they are related to the genotype.

Therefore, future studies should include patients with phenotypes similar to M-D but different monogenic causes. Moreover, larger groups of symptomatic and asymptomatic mutation carriers should be examined in comparison to healthy non-mutation carriers. Modulation of cerebellar activity of these participants via non-invasive plasticity induction could help to analyze the role of the cerebellum further. Furthermore, future studies should ideally aim for a

combination of clinical, neurophysiological, and imaging readout parameters. A correlation of clinical improvement with the modifiability of neurophysiological and imaging findings via plasticity induction might be helpful to explore disease-related mechanisms and guide the development of novel non-invasive treatment options.

Author contributions

FH contributed to data extraction and drafted and corrected the manuscript. SG contributed to data extraction and manuscript revising. AW contributed to data interpretation and to write, correct and revise the manuscript. AM contributed to correcting and revising the manuscript.

Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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