The Neurophysiological Features of Myoclonus-Dystonia and Differentiation From Other Dystonias

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**IMPORTANCE** Myoclonus-dystonia (M-D) is a clinical syndrome characterized by a combination of myoclonic jerks and mild to moderate dystonia. The syndrome is related to ε-sarcoglycan (SGCE) gene mutations in about half the typical cases. Whether the M-D phenotype reflects a primary dysfunction of the cerebellothalamocortical pathway or of the striatopallidothalamocortical pathway is unclear. The exact role of an additional cortical dysfunction in the pathogenesis of M-D is also unknown.

**OBJECTIVE** To clarify the neurophysiological features of M-D and discuss whether M-D due to SGCE deficiency differs from other primary dystonias.

**DESIGN, SETTING, AND PARTICIPANTS** We studied a referred sample of 12 patients with M-D (mean [SD] age, 28.8 [6.2] years; age range, 19-38 years; 5 women) belonging to 11 unrelated families with a proven mutation or deletion of the SGCE gene and a group of 12 age- and sex-matched healthy control individuals. Every participant underwent 3 sessions exploring the excitability of the primary motor cortex, the response of the primary motor cortex to a plasticity-inducing protocol, and the cerebellar-dependent eye-blink classic conditioning (EBCC). The clinical evaluation of patients included the Unified Myoclonus Rating Scale and Burke-Fahn-Marsden Dystonia Rating Scale.

**EXPOSURE** Myoclonus-dystonia with a proven SGCE mutation.

**MAIN OUTCOMES AND MEASURES** We measured resting and active motor thresholds, and short-interval intracortical inhibition and facilitation. The plasticity of the motor cortex was evaluated before and for 30 minutes after 600 pulses of rapid paired associative stimulation. The cerebellar functioning was evaluated with the number of conditioned responses during the 6 blocks of EBCC and 1 extinction block. All data were compared between the 2 groups. For patients, correlations were explored between electrophysiological data and clinical scores.

**RESULTS** We found lower membrane excitability of the corticocortical axons and normal intracortical γ-aminobutyric acid inhibition in contrast with what has been described in other forms of primary dystonia. Myoclonus-dystonia patients also shared some common pathophysiological features of dystonia, including enhanced responsiveness of the motor cortex to plasticity induction and abnormal response to cerebellar conditioning as tested by EBCC.

**CONCLUSIONS AND RELEVANCE** Specific underlying dysfunctions are associated with the very particular clinical phenotype of M-D and make it a unique entity that stands apart from other primary dystonias.
myoclonus-dystonia (M-D) is a clinical syndrome characterized by a combination of myoclonic jerks and mild to moderate dystonia.\(^1\) Mutation or deletion of the $\varepsilon$-sarcoglycan ($SGCE$ [OMIM 604149]) gene accounts for 40% to 50% of the cases with a typical phenotype.\(^2-4\) In 2011, a review of literature\(^5\) demonstrated that psychiatric disorders are also part of the phenotype, suggesting a more diffuse brain dysfunction than initially expected.

Whether the M-D phenotype in patients with the $SGCE$ mutation reflects a primary dysfunction of the cerebellathalamo-cortical pathway or of the striatopallidothalamocortical pathway is unclear. The exact role of an additional cortical dysfunction in the pathogenesis of M-D is also unknown. Myoclonus characteristics, namely, lack of stimulus sensitivity, a negative C-reflex finding, absence of premyoclonic cortical potential, and absence of giant somatosensory evoked potential, indicate subcortical origin.\(^6,7\) Among the subcortical structures, globus pallidus internus dysfunction might play a key role, because deep brain stimulation of the globus pallidus internus results in a marked improvement of myoclonus.\(^8,9\) Recording of local field potentials and single-cell activity during surgery also linked globus pallidus internus activity and myoclonus.\(^10-12\) In contrast, other neurophysiological findings\(^13\) and the results of recent morphological\(^14\) and functional\(^15,16\) imaging studies point to a dysfunction of the cerebellothalamocortical pathways. This finding is in keeping with the high expression level of the main brain-specific $SGCE$ isoform in the cerebellum.\(^4\)

Comprehensive neurophysiological investigation is a potent approach to understand the underlying pathophysiology of movement disorders. However, neurophysiological studies in M-D are scarce and involve small groups of patients, often belonging to a single family,\(^7,17,18\) or patients with heterogeneous genetic backgrounds.\(^6\)

The aim of this study was to clarify the neurophysiological characteristics of M-D, thereby gaining further insight into the pathophysiological features of the disease. Based on our findings, we discuss whether M-D due to $SGCE$ deficiency differs from other primary dystonias.

### Methods

#### Study Population

We studied 12 M-D patients (mean [SD] age, 28.8 [6.2] years; age range, 19-38 years; 5 women) from 11 unrelated families with a proven mutation or deletion of the $SGCE$ gene (DYT11 M-D). Patients with severe myoclonus or dystonia that interfered with recording were not included in the study. Severity of myoclonus was assessed by the Unified Myoclonus Rating Scale\(^19\) and that of dystonia, by the Burke-Fahn-Marsden Dystonia Rating Scale\(^20\) (Table 1). To ensure that the treatment would not interfere with the recordings, all pharmacological treatment was interrupted for at least 1 week before the beginning of the study. All variables were also recorded in 12 age- and sex-matched healthy volunteers (controls). The local ethics board approved the study. All participants gave written informed consent.

#### Study Design

Subjects came for 3 visits, separated by at least 1 week. Visit 1 included the clinical examination and rating, magnetic resonance imaging of the anatomical brain, and a battery of electrophysiological variables, including resting motor threshold (RMT) active motor threshold (AMT), short-interval intracortical inhibition (SICI), and short-interval intracortical facilitation (SICF). All electrophysiological variables were measured using a commercially available stimulator (BiStim\(^2\); Magstim

### Table 1. Clinical Features of Patients With M-D

<table>
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<th>Age, y/Sex</th>
<th>BFM Disability (0-29)</th>
<th>Movement (0-120)</th>
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<th>UMRS Subscale Score (Range)</th>
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Abbreviations: BFM, Burke-Fahn-Marsden Dystonia Rating Scale; M-D, myoclonus-dystonia; UMRS, Unified Myoclonus Rating Scale.

*Withdrawn at least 3 weeks before the study.

The last injection was more than 4 months before the study.
Company Ltd) that induces monophasic electrical pulses in the brain and a 7-cm figure-of-eight coil. Visit 2 included measurements of the RMT and AMT using another stimulator (Super Rapid² magnetic stimulator; Magstim Company Ltd) that generates biphasic electrical pulses in the brain (ie, rRMT and rAMT), and assessment of the left primary motor cortex (M1) responsiveness to rapid paired associative stimulation (RPAS). Visit 3 included the eye-blink classic conditioning (EBCC).

Electrophysiological Recordings
Participants underwent evaluation of their dominant hemisphere. During transcranial magnetic stimulation (TMS) experiments, surface electromyography (EMG) was recorded simultaneously from the abductor pollicis brevis (APB) and the abductor digitii minimi (ADM) muscles. The RPAS was the target muscle, whereas the ADM was the nontarget muscle with an adjacent cortical representation. The EMG signal was amplified and filtered (100–3000 Hz) with a commercially available ampliﬁer (D360; Digitim Ltd), then digitally transformed at a sampling rate of 10,000 Hz (CEDPower 1401MkII; CED Ltd) and stored offline for analysis (Signal software 4.02; CED Ltd). The EMG activity was continuously monitored during the recordings to ensure muscle relaxation. Trials contaminated by EMG activity anywhere within 500 milliseconds around each motor evoked potential (MEP) were discarded from the offline analysis. During the EBCC experiments, the surface EMG was recorded bilaterally from orbicularis oculi muscles.

Transcranial Magnetic Stimulation
Transcranial magnetic stimulation was conducted with a 7-cm figure-of-eight coil connected to the BiStim² module or the SuperRapid² magnetic stimulator. All stimulations were performed using a neuronavigation device (eXimia; Nextim Ltd) with individual anatomical magnetic resonance images. This process allowed maintaining the same placement and tilt of the stimulator coil throughout each session and from one session to the next in the same participant. The coil handle was oriented backward and laterally so that the first wave of the TMS pulse induced a posterior-anterior–directed current in the brain. The “hot-spot” for the APB was identified and marked on the individual 3-dimensional brain reconstructions as the point on the scalp over the M1 where MEPs had maximum amplitude for a given stimulation intensity.

Assessment of Threshold Corticospinal Excitability
The RMT was deﬁned as the minimal TMS intensity-eliciting MEPs of at least 50 μV in the resting target muscle in at least 50 of 10 consecutive trials. The AMT was deﬁned as the minimal TMS intensity-eliciting MEPs in the target muscle of at least 200 μV greater than the background EMG activity in at least 5 of 10 consecutive trials while the muscle was contracted isometrically to exert 20% of the maximum voluntary force.

Assessment of Inhibitory γ-Aminobutyric Acid–Secreting Interneuronal Circuits Within M1
The SICI was elicited with paired-TMS pulses, including a conditioning stimulus (CS₂₅) followed 2.5 milliseconds later by a test stimulus. The stimulation intensities for CS₂₅ were 70%, 80%, and 90% AMT, whereas intensity for the test stimulus was adjusted so that the single pulse would produce MEPs of 0.51 mV. The SICI was expressed as the mean peak-to-peak amplitude of all conditioned MEPs normalized to the mean amplitude of all unconditioned MEPs for each CS₂₅ intensity.

Assessment of Excitatory Circuits Within M1
The SICF was elicited with a suprathreshold first TMS pulse followed by a subthreshold second TMS pulse at intervals of 1.1, 3.2, 2.5, 3.3, and 4.3 milliseconds. In quantitative terms, the SICF was the mean amplitude of the conditioned responses (CRs) belonging to each time interval expressed as a percentage of the mean amplitude of all responses.

Assessment of M1 Spike-Timing-Dependent Plasticity
The plasticity-inducing protocol was a 5-Hz RPAS, which consisted of repeatedly pairing a peripheral electrical stimulation of the median nerve (intensity, 2.5 × the perceptual threshold) and a TMS subthreshold pulse (intensity, 90% of RMT) targeting the APB motor representation. The pulse pairs were repeated every 200 milliseconds (5 Hz) for 2 minutes (600 pairs). Each peripheral pulse was triggered 25 milliseconds before the TMS pulse. The paired associative stimulation with 25-millisecond pairing delay has been shown to induce a lasting increase in M1 excitability through hebbian-like associative plasticity that relies on mechanisms similar to long-term potentiation. The plastic effects were assessed by comparing the mean amplitude of 20 test MEPs measured before RPAS with those recorded every 5 minutes until 30 minutes after the RPAS end. The intensity of the test TMS pulses was set to evoke 0.5- to 1.0-mV MEPs before the intervention and kept unchanged after the intervention.

Eye Blink Classical Conditioning
The EBCC protocol is an associative learning paradigm, dependent on the cerebellum for acquisition. The CS was a tone (200-millisecond duration, 2-KHz pitch, and 50- to 70-dB intensity above the individual hearing threshold) played via binaural headphones, and the unconditioned stimulus (US) was an electrical stimulation (200-microsecond pulse width) of the right supraorbital nerve that evoked a stable reflex response (R2) bilaterally in the orbicularis oculi muscles. Repeated pairing of the CS with the US at 400-millisecond intervals leads to the gradual development of the eye-blink CR to the CS occurring within 200 milliseconds of US onset. The CS inconsistently produces an acoustic startle response (alpha blink) occurring within 200 milliseconds after CS onset.

The EBCC sessions consist of 6 learning blocks followed by 1 extinction block. Each learning block contained 9 trials with CS-US pairs, a 10th trial with US alone (to detect spontaneous blinks), and an 11th trial with CS alone (to verify that CRs are acquired independently of the US). The extinction block consisted of 11 CS-only trials. Occurrences of CRs within the CS-US interval were counted manually. The EMG bursts were considered alpha blinks if their amplitude exceeded 50 μV and if
latency was less than 200 milliseconds after the CS. The EMG bursts were considered CRs if latency was more than 200 milliseconds after the CS but before the US. Any EMG bursts occurring 200 to 600 milliseconds after the CS in the CS-only trials were considered CRs.

Statistical Analysis
We compared RMT, AMT, rRMT, and rAMT between M-D patients and healthy controls using unpaired *t* tests. Repeated-measures analysis of variance (rANOVA) was used to analyze the remaining electrophysiological variables with group (patients and controls) as the between-subjects factor and the following within-subjects factors: intensity (70%, 80%, and 90% AMT) for SICI; interstimulus interval (1.1, 3.2, 2.5, 3.3, and 4.3 milliseconds) for SICF; and time (pre-RPAS, 5, 10, 15, 20-25, and 30 minutes) for evaluating RPAS-induced effects. We used unpaired *t* tests for post hoc analysis.

To analyze CRs, we used rANOVA with block (blocks 1-6) as the repeated factor and group (patients and controls) as the between-subject factor. For the extinction block, we retained only data from participants who underwent successful conditioning (≥40% CRs in any block)27 and compared these between patients and controls using the 2-tailed unpaired *t* test.

We explored correlations between clinical scores and physiological variables by linear regression analysis. The RPAS-induced effects selected for the correlation were the overall condition (≥40% CRs in any block)27 and compared these between-subjects factor. For the extinction block, we retained only data from participants who underwent successful conditioning (≥40% CRs in any block)27 and compared these between patients and controls using the 2-tailed unpaired *t* test.

Results

Clinical Features
Action myoclonus in the upper limbs constituted the main symptom. Dystonia was absent in 3 patients and minimal in 4. The global disability score (scored on a visual analog scale ranging from normal [0] to severe disability [4]) had discrepant results between the patient self-rating and the neurologist rating (Table 1).

Motor Thresholds
When using monophasic TMS pulses, the RMT and AMT were similar between patients and controls. When using biphasic TMS pulses, the rAMT was significantly increased (*P* = .002) and the rRMT had a borderline increase (*P* = .07) in the patient group (Table 2). The biphasic thresholds correlated positively with the self-rated global disability score (rRMT: $R^2 = 0.62$, $r = 0.8$ [*$P* = .01]; rAMT: $R^2 = 0.51$, $r = 0.7$ [*$P* = .02]), but not with any other subscale score of the Burke-Fahn-Marsden Dystonia Rating Scale or the Unified Myoclonus Rating Scale (Figure 1A).

SICI and SICF
The SICI changed similarly with the conditioning stimulus intensity in patients and healthy controls for the APB and ADM (rANOVA: group, $F_{1,44} = 0.08$ [*$P* = .80]; intensity, $F_{2,44} = 32.7$ [*$P* < .001]; muscle, $F_{1,44} = 0.02$ [*$P* = .90]; no interactions) (Figure 1B). The SICF changed similarly with the interstimulus interval in patients and healthy controls for the APB and ADM (rANOVA: group, $F_{1,44} = 2.7$ [*$P* = .10]; interstimulus interval, $F_{5,44} = 13.3$ [*$P* < .001]; muscle, $F_{1,44} = 0.5$ [*$P* = .50]; no interactions) (Figure 1C).

Responsiveness of M1 to RPAS
The RPAS successfully induced a plastic change in M1 excitability in both groups, without a significant difference between the groups throughout the monitoring period (rANOVA: time, $F_{4,42} = 5.5$ [*$P* < .001]; group, $F_{1,42} = 1.8$ [*$P* = .20]; muscle, $F_{1,42} = 0.7$ [*$P* = .80]). However, we found a significant time × group interaction ($F_{4,4} = 6.1$ [*$P* < .001]), and post hoc comparisons between the patients and controls confirmed differences at 30 minutes (APB, $P = .05$; ADM, $P = .01$). This analysis showed that RPAS-induced plastic changes were similar in patients and controls until the peak at 20 minutes after the end of the intervention, after which M1 excitability returned to baseline levels in the controls at 30 minutes and remained at peak levels in patients (Figure 2A and B). Moreover, we found a borderline negative correlation between the self-rated global disability score and the RPAS-induced plasticity in APB globally ($R^2 = 0.34$, $r = -0.6$ [*$P* = .04]) (Figure 2C) and only at 30 minutes after the intervention ($r = -0.6$ [*$P* = .04]). We found no correlation with any other clinical score or for the ADM muscles.

Eye-Blink Classic Conditioning
Both groups showed a similar learning effect as the number of CRs increased from blocks 1 to 4, then plateaued to block 6 (rANOVA: block, $F_{5,19} = 24.4$ [*$P* < .001]; group, $F_{1,19} = 0.9$ [*$P* = .30]; no interaction, $F_{1,5} = 0.7$ [*$P* = .60]). Ten patients and
8 healthy controls acquired the CR, and we analyzed their extinction phases. Patients had a significantly lower extinction rate than controls, with 44% of CRs during the extinction block compared with 18% in the control group, whereas patients had 66% and controls had 64% of CRs during the last conditioning block (group, \(P = .2\); block, \(P < .001\); group \(\times\) block interaction, \(P = .02\); controls, post hoc t test, \(P < .01\)) (Figure 3).

The variation in motor evoked potential (MEP) amplitude after rapid paired associative stimulation (RPAS) is represented for each time point after intervention as a percentage of the mean baseline MEP amplitude. A, The MEP amplitude normalized to baseline for the abductor pollicis brevis muscle. B, The MEP amplitude normalized to baseline for the adductor digitii minimi muscle. C, Correlation between the mean MEP amplitude after RPAS and the self-rated global disability score. Dotted lines represent the 95% CI for the linear regression (solid line); dots, individual patients with myoclonus-dystonia (M-D).

\(a\) \(P = .05\), post hoc analysis.

\(b\) \(P = .01\), post hoc analysis.
Discussion

We conducted a controlled study investigating in detail the neurophysiological characteristics of 12 untreated M-D patients from 11 families with a proven SGCE defect. We found an enhanced AMT when measured with biphasic pulses but normal intracortical inhibition using γ-aminobutyric acid-secreting interneurons that is in contrast with what was described in other primary dystonias. Similarly to patients with other forms of dystonia, the M-D patients demonstrated the enhanced propensity of the motor cortex to develop plasticity and cerebellar dysfunction. Our findings indicate that specific underlying dysfunctions are associated with the very particular clinical phenotype of M-D and make it a unique entity that stands apart from other primary dystonias.

We found an enhanced motor threshold, commonly associated with abnormal membrane excitability of the cortical neurons. The increase of motor thresholds in M-D owing to SGCE deficiency has been controversial. Three previous studies found no abnormality in RMT or AMT using monophasic TMS pulses. Another study reported increased AMT in M-D patients belonging to a single family. Whether the findings were linked to M-D or represented a family trait was unclear. The present study was performed in a large number of unrelated M-D patients, thereby excluding the possibility of a family trait. A different methodological approach might explain the discrepancy between the studies. Indeed, we found an increased AMT only when we probed with biphasic TMS pulses. The RMT is a function of membrane potentials and of post-synaptic excitability levels at all the synapses en route to the spinal motoneurons. The AMT is closer to measuring membrane excitability, because synapses in the corticospinal chain are already activated by the voluntary contraction, and the membrane potentials are more homogeneous (close to the discharging threshold). Tentative explanation for the exclusive AMT increase after biphasic TMS stimulation is that biphasic pulses excite a more heterogeneous population of interneurons than monophasic ones that might be more susceptible to minute alterations of membrane excitability.

Augmented biphasic AMT correlated with the self-rated but not the neurologist-rated global disability score of the Unified Myoclonus Rating Scale. This finding was unexpected. The self-rated score might provide a better estimation of disease severity, because M-D symptoms vary throughout the day and the Unified Myoclonus Rating Scale scoring by a neurologist may fail to evaluate in its entirety the real impact of myoclonus in daily life.

The SICI and SICF were normal in our M-D patients, confirming previous findings, with the single exception that found a decrease in the SICI when measured at a 3-millisecond interstimulus interval. In contrast, inhibition of γ-aminobutyric acid secretion is abnormal in primary and focal dystonia. Whether normal SICI in M-D and decreased SICI in focal dystonia reflect different pathogenic underpinnings in both disorders remains unclear. The bilateral decrease of SICI in focal hand dystonia despite unilateral symptoms may reflect a primary dysfunction of the dystonic brain. However, decreased SICI in psychogenic dystonia suggested the opposite; it may be the consequence of dystonic movements per se. If true, then the normal SICI in M-D patients would only reflect the paucity of dystonic posture/movements.

We found abnormal plasticity of the motor cortex in M-D patients, which is a core feature of dystonia. When testing the sensorimotor associative plasticity, the RPAS triggered an increase in M1 excitability, which was not higher but outlasted the effect observed in controls. This profile was strikingly similarly to the profile triggered by RPAS in focal hand dystonia. Abnormal plastic responses in focal or generalized dystonia were also reported using various plasticity-inducing protocols. Intriguingly, the mean RPAS effect and the level of M1 excitability at 30-minute post-RPAS correlated with the self-rated global disability score, whereby higher RPAS-induced effects resulted in a less severe disability score. A possible explanation is that enhanced M1 responsiveness to the RPAS is a true endophenotypic trait that is detected only in less severely affected patients (ie, who rarely have myoclonus jerks at rest) and concealed by the subjacent myoclonic jerks in more severely
affected patients. Indeed, muscle activity preceding the application of a plasticity-inducing protocol can interfere with or even suppress the plasticity-inducing process.\textsuperscript{37}

When testing the integrity of cerebellar mechanisms controlling associative learning, we found that the EBCC was acquired similarly in patients and controls but failed to be extinguished efficiently in M-D patients, who maintained higher rates of CR compared with controls. This finding differs from the severe impairment of acquisition and extinction of conditioning in focal dystonia,\textsuperscript{37,38} pointing to different subcortical mechanisms. Although acquisition and extinction of CR involve the cerebellum, their underlying neuronal substrates are likely different.\textsuperscript{39} Long-term depression/potentiation at the synapses of the parallel fibers and Purkinje cells seems to support maintenance of acquisition of the CR and relies heavily on the inferior olive and deep cerebellar nuclei.\textsuperscript{39-41} Extinction of the CR is an active inhibitory process that might rely more on the cerebellar cortex and the external inputs to the cerebellum.\textsuperscript{39} Despite the clinical absence of ataxia or cerebellar tremor, cerebellar dysfunction in manifesting M-D is supported by neuroimaging studies demonstrating hyperactivation of the anterior cerebellum in functional magnetic resonance imaging tasks\textsuperscript{46} and increased metabolism in the parasagittal cerebellum.\textsuperscript{49} Cerebellar dysfunction is also supported by the failure of M-D patients to adapt their saccades during a backward-reactive adaptation task.\textsuperscript{13} Key neuronal circuits supporting this task were located in the dorsal vermian lobules and the fastigial nucleus.

**Conclusions**

The lack of cerebellar cardinal signs in dystonia despite neurophysiological evidence of cerebellar dysfunction might reflect a distortion of the cerebellar output. In contrast, a reduction of the cerebellar output would lead to a loss of function and overt cerebellar clinical manifestations.\textsuperscript{19,20} The present results further support that a dysfunction of the cerebellum participates in the pathophysiology of dystonia irrespective of the type (sporadic focal dystonia, DYT1 generalized dystonia, or DYT1 M-D). In keeping with this model, the severity and location of cerebellar dysfunction might account for the different phenotypes.\textsuperscript{43} These results give physiological support to previous neuroimaging findings by pointing to a possible involvement of the parasagittal cerebellum in the pathogenesis of M-D.