Clinical Neurophysiology 156 (2023) 125–139

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Rethinking the neurophysiological concept of cortical myoclonus

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HIGHLIGHTS

- Evidence supporting the electrophysiological criteria of cortical myoclonus is not very solid.
- Although they can be useful if properly used, the electrophysiological criteria of cortical myoclonus should be reviewed.
- Combining more than one test, together with clinical features, may increase the diagnostic accuracy of cortical myoclonus.

ARTICLE INFO

Article history:
Accepted 13 October 2023
Available online

Keywords:
Myoclonus
Cortical myoclonus
Neurophysiology
Jerk-lock back averaging
Giant SEP
C-reflex

ABSTRACT

Cortical myoclonus is thought to result from abnormal electrical discharges arising in the sensorimotor cortex. Given the ease of recording of cortical discharges, electrophysiological features of cortical myoclonus have been better characterized than those of subcortical forms, and electrophysiological criteria for cortical myoclonus have been proposed. These include the presence of giant somatosensory evoked potentials, enhanced long-latency reflexes, electroencephalographic discharges time-locked to individual myoclonic jerks and significant cortico-muscular connectivity. Other features that are assumed to support the cortical origin of myoclonus are short-duration electromyographic bursts, the presence of both positive and negative myoclonus and cranial-caudal progression of the jerks. While these criteria are widely used in clinical practice and research settings, their application can be difficult in practice and, as a result, they are fulfilled only by a minority of patients. In this review we reappraise the evidence that led to the definition of the electrophysiological criteria of cortical myoclonus, highlighting possible methodological incongruencies and misconceptions. We believe that, at present, the diagnostic accuracy of cortical myoclonus can be increased only by combining observations from multiple tests, according to their pathophysiological rationale; nevertheless, larger studies are needed to standardise the methods, to resolve methodological issues, to establish the diagnostic criteria sensitivity and specificity and to develop further methods that might be useful to clarify the pathophysiology of myoclonus.

Contents

Abbreviations: CM, cortical myoclonus; CBS, corticobasal syndrome; CMC, cortico-muscular coherence; EMG, electromyography; EEG, electroencephalography; EPC, epilepsia partialis continua; HD, Huntington's disease; HFO, high frequency oscillations; JLBA, jerk-locked back averaging; LLR, long-latency reflexes; M1, primary motor cortex; PD, Parkinson's disease; SEP, somatosensory evoked potentials.

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https://doi.org/10.1016/j.clinph.2023.10.007
1388-2457/

1. Introduction

Brief muscle jerks, caused by abrupt muscle contraction or sudden cessation of ongoing muscular activity, without the random flow of chorea or the stereotypy of tics, are called myoclonus. Myoclonus is produced by abnormal discharges at different levels of the central or peripheral nervous system, and its clinical presentation differs according to its neural generator. The most common subtype is cortical myoclonus (CM), that is caused by abnormal discharges arising in the sensorimotor cortex (Kojovic et al., 2011; Shibasaki and Hallett, 2005). Given the ease of cortical recordings, electrophysiological features of CM have been better characterized than those of subcortical forms (Shibasaki and Thompson, 2011); nevertheless, as we have recently suggested (Latorre et al., 2018a), the application of current electrophysiological criteria for CM is difficult in practice and, although their physiological rationale is clear, they are fulfilled only by a minority of patients.

Typically, CM clinically manifests with shock-like jerks affecting the distal limbs or the face; it is often action-induced, positive and negative, and sensitive to somatosensory stimuli (Shibasaki and Hallett, 2005). Electrophysiology can supply additional evidence for the cortical origin of myoclonus (Latorre et al., 2018b). According to the current literature, features suggestive of a cortical origin in CM are short electromyographic (EMG) bursts duration (<50 ms), the presence of both positive and negative myoclonus, and cranial-caudal progression of the jerks (Latorre et al., 2018a; Shibasaki and Hallett, 2005). Definitive features that confirm a cortical generator of the jerks are the presence of giant somatosensory evoked potentials (SEP), pathological long-latency reflexes (LLR), commonly referred to as the C-reflex, electroencephalographic (EEG) discharges time-locked to individual myoclonic jerks detected with jerk-locked back averaging (JLBA), and significant cortico-muscular connectivity (Shibasaki and Thompson, 2011). These tests are widely used in clinical practice and research settings (Latorre et al., 2018a; Merchant et al., 2020; Zutt et al., 2018) and have been proven to increase the diagnostic yield of CM (Everlo et al., 2022; van der Veen et al., 2021; Zutt et al., 2018); despite this, we believe that they present several weakness that may lead to questionable diagnoses.

The aim of this paper is to reappraise the evidence that led to the definition of the electrophysiological criteria for CM. We critically review their application in previous studies, to understand better the evidence that supports their diagnostic role and to highlight possible methodological incongruencies and misconceptions. We have found that the available evidence is, in general, too weak to consider the electrophysiological criteria for CM as "definitive". However, we argue that their specificity might be increased by combining observations from multiple tests, according to their pathophysiological rationale.

2. Giant somatosensory evoked potentials

SEPs are time- and phase-locked EEG responses which assess the dorsal column–lemniscal system function. Stimulation of the median nerve is used most commonly to evoke SEP. The cortical response is recorded from parietal scalp electrodes and shows a negative wave at 20 ms (N20) and a positive wave at 25 ms (P25) arising from the primary somatosensory cortex, followed by a negative wave at 33 ms (N33) reflecting precentral activation (Cruccu et al., 2008; Rocchi et al., 2017).

Dawson, in 1947, provided the first evidence that the sensorimotor cortex can be involved in myoclonus. He recorded a large evoked potential over the sensorimotor scalp following either tendon taps or electrical stimulation of popliteal or ulnar nerves, both of which provoked a generalised myoclonic jerk several milliseconds later. The amplitude of the response was 5 to 10 times larger than in healthy volunteers, albeit with a similar shape and latency (Dawson, 1947). Later studies in larger populations confirmed the association between the presence of a large SEP and myoclonic jerks, and it was proposed that the presence of "giant" SEP could be used as a marker to distinguish cortical from subcortical forms (Halliday, 1967; Rothwell et al., 1984; Shibasaki, 2006; Shibasaki et al., 1985a; Shibasaki et al., 1985b; Sutton and Mayer, 1974). However, not only CM can occur in the absence of enlarged SEPs, but the latter can be present in subjects without CM.

2.1. "Giant" SEPs and myoclonic jerks: Technical issues

Before considering the neurophysiology of the "giant" SEP, there are two technical issues to note. First, there is no definition of "giant" SEP. In the early studies, the amplitude of the P25/N33 SEP components was considered suggestive of CM when found to be far above those seen in normal subjects (Obeso et al., 1985; Rothwell et al., 1984; Shibasaki et al., 1978). Shibasaki and colleagues defined SEP as giant when the P25 was larger than 8.6 μV or the N33 was larger than 8.4 μV, based on previous data in healthy controls and patients with cerebral lesions of various etiologies (Shibasaki et al., 1977). Another definition often used in the literature is an amplitude greater than the average plus 2–

Table 1
Summary of the studies considered where SEP was performed.

Study	Definition of Giant	Disease	-Stim. Nerve- Stim. Frequency- Intensity of Stim.	N of patients with giant responses/total tested (%)	Giant SEP amplitude
Shibasaki et al., 1978	NA (compared to HS)	PME	Median ISI 1–3 s 10–15% >MT	13/14 (93%)	N33: 12–75 μV (av. 41 μV)
Rothwell et al., 1984	NA (compared to HS)	Head trauma/unknown	Digital ISI 2–3.5 s 1.5 x ST	4/4 (100%)	P1/N2 (∼P25/N33): 12–54 μV
Obeso et al., 1985	NA (compared to HS)	MSA-C, EOCA, DCM, post-traumatic, unknown	Digital ISI 2–3.5 s 2 x ST	10/11 (91%)	P1/N2 (∼P25/N33): 10–45 μV
Shibasaki et al., 1985a, 1985b	N20/P25 > 8.6 μV, P25/N33 > 8.4 8.6 μV	PME and related disorders, PA, OMS, CJD, epilepsy with myoclonus, EM, oculo-palatal-somatic, spinal, and others	Median 1 Hz 10% >MT	24 (23/27 PME, 1/3 CJD)/50 (48%)	P25/N33: 34–63 μV
So et al., 1989	>3 SDs of the responses established in a sample of HS	MERRF	NA (wrist and ankle) NA NA	4/6 (67%)	NA
Brown et al., 1991	NA	PA, PMA, HD, CD	Median NA slightly > MT	3 (PMA, CD)/9 (33%)	P1/N2 (∼P25/N33): 7.5–50 μV
Rodriguez et al., 1994	N20/P25 or P25/N3 > 10 μV	MSA-C	Digital ISI 2–3.5 s 1.5 x ST	15/23 (65%)	N20/P25: 3–25 μV P25/N33: 1.2–31.2 μV
Thompson et al., 1994a, 1994b, 1994c	P25-N30 amplitude > 10 μV	CBS	Median/digital NA NA	1/13 (8%)	P1/N2 (∼P25/N33): 11.5 μV
Thompson et al., 1994a, 1994b, 1994c	NA	HD	Wrist ∼1Hz slightly > MT	0/3	NA
Ikeda et al., 1995	N20 > 7.6 μV, P25> 6.3 μV, N30 8.8 μV, N35 > 9.8 μV (mean + 3SD of the logarithm of the values obtained in HS)	PME	Median Hz 10% >MT	4/4 (100%)	N20: 2.2––5.2 μV P25: 3.7–13.6 μV N30: 6.9–30.5 μV N35: 5.2–32.0 μV
Terada et al., 1997	>av. + 3 SDs after logarithmic transformation of normative values	BAFME	Median Hz 10% >MT	6/6 (100%)	P25: 3.9–27.1 μV N33: 4.3–68.3 μV
Caviness and Kurth, 1997	>12 μV	HD	Median 1.5 Hz Muscle twitch	1/1 (100%)	N20-P30: 20.4 μV
Lu et al., 1998	NA	CBS	Median Hz Muscle twitch	0/2(but 1 defined as enlarged)	Enlarged SEP: N20: 9.17 (L), 7.94 (R) μV; P25: 17.50 (L), 14.38 (R) μV

(*continued on next page*)

Table 1 (*continued*)

Study	Definition of Giant	Disease	-Stim. Nerve- Stim. Frequency- Intensity of Stim.	N of patients with giant responses/total tested (%)	Giant SEP amplitude
Brown et al., 1999	NA	PMA, PA, CD	Median/tibial NA NA	2 (CD)/8 (25%)	NA
Caviness et al., 2002	>11.1 μV (>av + 2.5 SD of normative values) for P25-N33 in patients older than 60 year-old	PD	Median 1.5 Hz Muscle twitch	0/20	P25-N33: 3.1 ± 2.9 μV (range, 0.34–10.2)
Okuma et al., 2005	NA	MSA	Median ~ 2 Hz NA	0/11 (but 3 defined as enlarged)	N20-P25: 7.2 ± 3.1 μV (enlarged > 10 μV)
Hitomi et al., 2011	>3 SDs of values obtained from the control subjects < 50 years old (P25 > 10.0 μV or N35 > 8.1 μV) and > 50 years old (P25 > 20.0 μV or N35 > 14.8 μV)	BAFME	Median 1 Hz Muscle twitch	13/16 (81%)	P25: 11.4 ± 6.1 μV N35: 19.2 ± 11.5 μV
Visani et al., 2013	N20/P25 and P25/N33 both > av. + 3SDs normative values (12.3 μV for N20/P25, and 8.6 μV for P25/N33)	ULD	Median 1 Hz slightly > MT	13/25 (52%)	N20/P25: 13.3–38.9 μV P25/N33: 11.3–67.3 μV
Van Egmond et al., 2014	NA	PMA (due to GOSR2 mutation)	NA NA NA	1/5 (25%)	NA
Storti et al., 2017	NA	PME	Median 2 Hz Muscle twitch	4/4 (100%)	N20-P25: 26.2 ± 8.2 μV (right), 27.9 ± 3.7 μV (left)
Canafoglia et al., 2017	>av. + 2SD of the normative values (N20-P25: 7.0 ± 3.6 μV; P25-N33: 2.8 ± 2.5 μV	Dravet syndrome	Median 1 Hz NA	1/19 (5%)	NA
Zutt et al., 2018	P27 and N35 > 5 μV and had a suitable shape	PMA, PME, NPC, HD etc.	NA NA NA	3/14 (21%)	NA
Tojima et al., 2021	P25 > 6.3 μV or N35 > 9.8 μV on either side	BAFME, ULD, CBS, PME of unknown aetiology etc.	Median 16.1 Hz 120% of MT	16 (BAFME), 33 others/49 (100%)	BAFME: P25: 17.6 ± 6.6 μV N35: 31.9 ± 15.0 μV Others: P25: 15.3 ± 9.7 μV N35: 15.8 ± 14.7 μV

Av.: average, BAFME: Benign adult familial myoclonus epilepsy, CD: coeliac disease, CJD: Creutzfeldt-Jakob disease, DCM: dyssynergia cerebellans myoclonica, EOCA: early onset cerebellar ataxia, EM: essential myoclonus, ISI: interstimulus interval, L: left, MERF: myoclonus epilepsy and ragged-red fibres, MSA: multiple system atrophy, MT: motor threshold; NA: not available, PA: post-anoxic, NPC: Niemann-Pick type, PD: Parkinson's disease, PMA: progressive myoclonic ataxia, PME: progressive myoclonic epilepsy, R: right, SEP: somatosensory evoked potentials, Stim.: stimulated/stimulation, ST: sensory threshold, ULD: Unverricht–Lundborg disease.

3 times the standard deviation of healthy subjects' responses (Canafoglia et al., 2017; Caviness et al., 2002; Hitomi et al., 2011; Ikeda et al., 1995; So et al., 1989; Terada et al., 1997; Visani et al., 2013). In other studies, the cut-off for giant SEP is arbitrary (e.g., 5 (Zutt et al., 2018) or 10 μV (Rodriguez et al., 1994; Thompson et al., 1994c)) or not mentioned at all (Brown et al., 1991; Lu et al., 1998; Okuma et al., 2005; Storti et al., 2017; Thompson et al., 1994c; van Egmond et al., 2014). Moreover, the definition of giant relies on the presence of increased amplitude of both N20-P25 and P25-N33 components in some work, while only one enlarged component is considered satisfactory elsewhere. Some examples of these criteria are listed in Table 1.

A second problem is that there is no consistency on how to measure SEP amplitudes, which could be peak-to-peak or baseline to peak. This might be relevant since in the peak-to-peak analysis the P25 peak is present in both N20-P25 and P25-N33 components and it gives higher values compared to baseline to peak. Furthermore, SEP amplitude might also be influenced by physical factors such as brain state or skull thickness; however, these are unlikely to explain the variable SEP amplitude systematically observed in CM across the studies.

It is relevant to mention that most patients have been studied while taking pharmacological treatment acting on the central nervous system, which could influence SEP amplitude (in either direction or reducing it, like Perampanel (Oi et al., 2019)), causing a bias in the interpretation of the data. However, this might not be true for all drugs: for instance, Rothwell and colleagues suggested that IV Lisuride and Clonazepam can reduce the severity of myoclonic herks leaving the amplitude of the SEP unchanged (Rothwell et al., 1984).

2.2. The link between giant SEPs and myoclonic jerks

It is clear that giant SEPs are not universally seen in patients presumed to have CM, but this variability seems unrelated to any clinical factor. When comparing 57 patients affected by different myoclonic disorders, Shibasaki and colleagues found that SEPs were giant in most cases of progressive myoclonus epilepsy, in post-hypoxic myoclonus and only one case of Creutzfeldt-Jakob disease, but not in the others (including opsoclonus-myoclonus syndrome, epilepsy with myoclonus, essential myoclonus) (Shibasaki et al., 1985b). It might be argued that in those without giant SEPs the myoclonus was subcortical; however, some of these patients had a cortical pre-myoclonic correlate detected with JLBA technique (Shibasaki et al., 1985b). Giant SEPs seem to be more prevalent in myoclonic epileptic disorders, including benign adult familial myoclonus epilepsy (Latorre et al., 2018a), which also has a significantly larger N33 component compared to other CM disease (Tojima et al., 2021); however, this finding is not consistent and can vary even in family members affected by the same condition (Terada et al., 1997; van Rootselaar et al., 2005). This variability can also be seen in basal ganglia disorders, in which CM can have different electrophysiological features from those encountered typically in epileptic syndromes. In Parkinson's disease (PD) and Lewy body dementia, SEPs have been considered as normal (Caviness et al., 2002; Caviness et al., 2003), while in minipolymyoclonus of multiple system atrophy they were enlarged (Okuma et al., 2005; Rodriguez et al., 1994); in Huntington's disease (HD) they have been reported as either normal or giant (Caviness and Kurth, 1997; Thompson et al., 1994a). In corticobasal syndrome (CBS), in which CM is a common distinctive feature, SEPs have rarely been found enlarged although they often have an abnormal morphology on both myoclonic and non-myoclonic sides, with loss of the parietal P25 and N33 components (Carella et al., 1997; Thompson et al., 1994c). Nevertheless, in a recent study, 67% patients with CBS were found to have giant SEP with normal morphology (Latorre et al., 2018a). The reason for this inconsistency among and within disorders is not clear and does not seem related to the presence of stimulus sensitivity or other clinical factors, although data on these aspects are scarce. Overall, according to two recent studies, only 21% (Zutt et al., 2018) and 39% (Latorre et al., 2018a) of patients with presumed CM showed giant SEPs, which seems a relatively small number for what is considered a definite diagnostic criterion.

Another important puzzling aspect is that giant SEPs are not specific for CM and can be observed in several conditions in the absence of myoclonus, including progressive supranuclear palsy, multiple sclerosis, pain, motor neuron disease and functional neurological disorders (Abbruzzese et al., 1991; Horlings et al., 2020; Kofler et al., 2000; Rossi Sebastiano et al., 2022). No clear differences have been found between enlarged/giant SEP in non-myoclonic conditions and CM, although this has not been systematically reviewed. According to one study (Abbruzzese et al., 1991), it is possible that enlarged/giant SEP in progressive supranuclear palsy affect both N20-P25 and P25-N33 components rather than only the latter, a pattern most often observed in conditions such as benign adult familial myoclonus epilepsy (Tojima et al., 2021). Furthermore, SEPs were enlarged in both hemispheres in a patient with unilateral CM (Rocchi et al., 2019) and in pre-symptomatic members affected by benign adult familial myoclonus epilepsy, who developed myoclonus 1.5 years later (Striano et al., 2005). All these observations suggest that the hyperexcitability of the sensorimotor cortex, as reflected by giant SEP, may not be directly linked to the clinical manifestation of the jerks, and question the pathogenic role of these responses in this context. This is also supported by the lack of correlation between the improvement of myoclonus and SEP amplitude and the clinical myoclonus score after treatment (Oi et al., 2019; Rothwell et al., 1984; Shibasaki et al., 1985b), as well as by the absence of parallel changes between SEP amplitude and severity of the myoclonus during disease progression (Hitomi et al., 2011; Kobayashi et al., 2014).

2.3. The pathophysiology of giant SEP

Two key questions surround the role of the giant SEP in myoclonus: its source in the brain and its underlying pathophysiology. The similarity of its latency and form to that of the normal SEP suggest that its source lies in the primary somatosensory area (S1), with the area 3b being the most likely site. Area 3a, which receives proprioceptive afferents, may also be involved, as well as the primary motor cortex (M1) (Hitomi et al., 2006) and supplementary motor areas (Visani et al., 2013) as suggested by occasional reports.

In most patients, the initial N20 component of the giant SEP is not enlarged, indicating that the initial thalamo-cortical input, which arrives in area 3b (or 3a if muscle afferents are stimulated), is processed normally. It is the later P25-N33 components that are enlarged and thought to reflect activity in area 1, which receives input from area 3b and from later arriving inputs in both slower conducting afferents and in more indirect pathways (such as via the cerebellum) (Rothwell et al., 1984).

It has been proposed that the giant SEP is caused by a general lack of inhibition (Visani et al., 2013), perhaps caused by reduced cerebellar inhibition (Latorre et al., 2020), hyper-synchronisation of abnormally firing neurons (Ikeda et al., 1990; Nakatani-Enomoto et al., 2016), or the existence of a preferential connection between the thalamus and S1 (Storti et al., 2017). Moreover, a thalamic contribution to the giant SEP, in addition to cortical hyperexcitability, has been supported by growing evidence of abnormal SEP-related high frequency oscillations (HFO) in some types of myoclonic epilepsies (Alegre et al., 2006; Assenza et al., 2020; Tojima et al., 2021). High frequency components (>400 Hz) of SEP are thought to reflect activity in thalamo-cortical circuits as

well as early inhibitory cortical responses (Rocchi et al., 2016; Rocchi et al., 2017). A suppression of the post-synaptic (late) component of HFO, related to cortical inhibitory interneuronal activity, has been found in epilepsia partialis continua (EPC), a form of CM (Insola et al., 2019); this suggests that giant SEPs seen in EPC might be related to a dysfunction of Gabaergic interneurons of a cortical sensory-motor network. Evidence of reduced sensorimotor cortical inhibition comes also from transcranial magnetic stimulation studies as shown below (Dubbioso et al., 2022; Hanajima et al., 2008; Nardone et al., 2018). Nevertheless, the underlying mechanisms causing this hyperexcitability are still far from being understood. Whatever the pathophysiology of the giant SEP, the fact that it most probably arises in S1 can explain the lack of obligatory coupling with myoclonic jerks. M1 is the source of the majority of corticospinal motor fibres, so it is conceivable that in some cases the abnormal sensory cortex activity "drives" an abnormal, and highly synchronised motor output, whereas in other cases, this link is less stable, and giant SEPs can occur without producing a jerk.

Other applications of SEP that support sensorimotor cortex hyperexcitability in CM have been proposed, but so far applied only in few studies. One is the SEP recovery cycle which, even in patients with CM and normal SEP amplitude, can show reduced SEP suppression at short interstimulus interval, reflecting a lack of intracortical inhibition (Dubbioso et al., 2022; Ugawa et al., 1991). The second is the use of brain electrical source analysis to investigate the topographical distribution of early scalp SEP (Valeriani et al., 1997). A wider application of these techniques is warranted in future to understand their potential role in the diagnosis of CM.

3. Long-latency reflex (C-reflex)

LLRs are long-latency hand-muscle reflexes likely mediated by transcortical pathways. They are usually assessed in the thenar muscles after median nerve stimulation and include up to three distinct responses termed LLR I (35–46 ms), II (45–58 ms), and III (>68 ms) (Cruccu and Deuschl, 2000).

While assessing the H reflex in one patient with reflex CM, Sutton and Mayer observed a consistent late response with a mean latency of 51 ms and similar shape and duration to those recorded during spontaneous myoclonic jerks (Sutton and Mayer, 1974). By subtracting the F wave latency, the authors estimated that the last 24 ms of this LLR reflected conduction across central pathways and named it the "C-reflex" (Sutton and Mayer, 1974). After its first description, the C-reflex has been considered one of the pathophysiological hallmarks of CM, but there are several unsolved questions regarding its nomenclature, reproducibility, specificity, and anatomical correlates (Table 2).

3.1. The correspondence between C-reflex and physiological LLR

C-reflex nomenclature is ambiguous, and this makes the boundaries between physiological LLRs and pathological C-reflex uncertain. While Sutton and Mayer described the C-reflex as a pathological reflex characteristic of CM, subsequent studies described it as "enhanced" or "exaggerated" (Okuma et al., 2005, Terada et al., 1997, Tobimatsu et al., 1985), without clarifying their significance. It has been suggested that the physiological counterpart of C-reflex is the early component of LLR, namely LLR-I (Cassim and Houdayer, 2006) (Cruccu and Deuschl, 2000). In normal subjects, LLR-I can be observed only during muscle contraction (Deuschl, 2003), whereas the C-reflex has been described at rest in patients with myoclonus, suggesting hyperexcitability of the sensorimotor cortex (Avanzini et al., 2016). However, the overlap between C-reflex and LLR-I is uncertain. LLR-I latency is about 40 ms, whereas C-reflex latency ranges from 39 (Shibasaki et al., 1978) to 55. 3 ms (Salazar et al., 2000), meaning that, in some patients, the C-reflex might correspond to the later peak LLR-II rather than to LLR-I. This is not a merely classification difference, given that distinct neural pathways are thought to underlie LLR-I and LLR-II in humans (Cruccu and Deuschl, 2000).

3.2. C-reflex and myoclonic jerks: Technical issues

The methodology used to assess the C-reflex differs in terms of stimulation (stimulus intensity, rate and pulse width) and recording (type and number of muscles) across studies, and only two studies included a control group, showing different results (Chen et al., 1992, Rodriguez et al., 1994). In one, the authors investigated LLR in parkinsonism associated with myoclonus and found an exaggerated late response compared with healthy subjects (Chen et al., 1992). In the other study, the C -reflex was assessed in multiple system atrophy type C with reflex myoclonus and in healthy subjects, and the C-reflex was observed only in some patients (Rodriguez et al., 1994).

Moreover, although the C-reflex is considered a key element for the neurophysiological diagnosis of CM, its reproducibility has not been tested extensively. In some studies, the C-reflex was tested in a smaller number of patients compared to SEPs and JLBA (Rodriguez et al., 1994, Shibasaki et al., 1985b); in others, it was not specified whether the number of patients who showed a C-reflex corresponded to the whole population in which C-reflex had been tested (Shibasaki et al., 1978). From those studies in which this information was mentioned, the C-reflex seems to occur in a variable percentage of CM patients (56% (Latorre et al., 2018a) – 100% (Uozumi et al., 2008)).

3.3. The pathophysiology of C-reflex

The disease- and myoclonus type-specificity of the C-reflex is unclear. The initial hypothesis was that the C-reflex is specific for reflex CM, but several observations challenge this theory. It is known that the LLR can be abnormal in other movement disorders not presenting with myoclonus, including PD (Fuhr et al., 1992), dystonia (Naumann and Reiners, 1997) and essential tremor (Deuschl et al., 1987); additionally, the C-reflex can be observed in other forms of myoclonus "no matter whether their origin is cortical or subcortical", as stated by Deuschl and Lucking (1990) (Deuschl and Lucking, 1990) (for example, in reticular myoclonus (Hallett et al., 1977)).

A further issue concerns the anatomical structures that underlie C-reflex generation. Sutton and Mayer hypothesized a transcortical origin of the C-reflex, indirectly confirmed by studies assessing the relationship between the C-reflex and giant SEPs in myoclonus. The authors found that the time interval from myoclonus-related cortical spike to the onset of the spontaneous myoclonus was almost identical to that from the N33 to the C-reflex, suggesting that the C-reflex represents the neurophysiological correlate of CM (Shibasaki and Hallett, 2005, Shibasaki et al., 1978). Overall, the findings support an involvement of the sensorimotor cortex in C-reflex generation (Shibasaki et al., 1978, Shibasaki et al., 1985b); however, the anatomical pathway has not yet been elucidated and it is unclear whether it is the afferent, afferent-efferent or efferent tract of C-reflex circuit that is hyperexcitable in CM.

4. Jerk-locked back averaging

Jerk-locked back averaging is an extension of EEG–EMG polygraphy and consists of averaging EEG signals in a time window prior to the myoclonic bursts. The assumption is that all EEG information which

Table 2
Summary of the studies considered where C-reflex was performed.

Study	Overall sample (sample size)	Methods	Latency in ms (range)	C-reflex/total tested (%)	Main findings regarding long-latency reflex
Shibasaki et al., 1978	30 PME (14), epilepsy with myoclonus (3), EM (4), SSE (2), midbrain infarction (2), others (5)	Stimulation site: median nerve at wrist Stimulus intensity adjusted to 10–15% above the threshold for contraction of the opponents pollicis muscle Stimulation rate: ISI between 1 and 3 s, random Recording: surface EMG from thenar muscle	39 (35–42)	8 PME/NA	Recorded from the stimulated (C) and non-stimulated side (C') Similar C–C' and N33-N33′ latency interval Interval from spike to myoclonus similar to that from N33 to C-reflex
Shibasaki et al., 1985a, 1985b	61 PME and allied diseases (27), sialidase and β-galactosidase deficiency (3), sialidase deficiency (1), opsoclonus-polymyoclonia syndrome (1), CJD (3), epilepsy with myoclonus (9), EM (5), oculo-palatal-somatic myoclonus (2), spinal myoclonus (2), others (8)	Stimulation site: median nerve at wrist Stimulus intensity: adjusted to 10% of motor threshold Stimulation rate: 1 Hz, random Recording: surface EMG from thenar muscle of the stimulated side (other muscles as necessary)	NA (31–58)	21 PME +1CJD/32 (69%)	The 21 patients with PME who showed an enhanced C-reflex had giant SEPs Six patients with PME and allied diseases showed double positive peaks of giant SEPs and double C-reflexes The latency difference between the two positive SEP peaks was approximately 25 ms and was very close to that between the two C-reflexes (C1 and C2) The time interval from the first positive peak of the giant SEP to C1 was equal to that from the second positive peak of the giant SEP to C2
Chen et al., 1992	26 HS (11), PD (5), stimulus-sensitive myoclonus associated with akinetic rigid syndrome (10)	E2 Stimulation site: median nerve at middle finger Stimulus intensity: equal to perceptive threshold Stimulation rate: five pulses at 500 Hz at random intervals between 1 s and 1.5 s Pulse width: 200 μs Recording: surface EMG from thenar muscles	63.5	NA	E2 response rather than C reflex was recorded
Rodriguez et al., 1994	53 OPCA (23), HS (30)	Stimulation site: median nerve at wrist Stimulation rate: <0.5 Hz, 0–1 ms duration Recording: surface EMG electrodes placed on the forearm flexor and extensor muscles	39.9 (30–50)	16/23 (70%)	All patients with C-reflex had giant SEPs

(*continued on next page*)

Table 2 (*continued*)

Study	Overall sample (sample size)	Methods	Latency in ms (range)	C-reflex/total tested (%)	Main findings regarding long-latency reflex
Salazar et al., 2000	11 MSA-P (11)	Stimulation site: digital nerve Stimulus intensity: 3 times the sensory perception threshold Stimulus intensity and rate and width: not reported Recording: surface EMG from wrist flexor/estensor muscles and thenar muscles (3 patients)	55.3 (50–63)	NA	No definition of the type of long-latency reflex studied The latency of the responses recorded was within the range of the cutaneo-muscular reflexes LLR II or E2 responses of the forearm and hand muscles
Caviness et al., 2002	20 PD with small-amplitude myoclonus (20)	Stimulation site: median nerve at wrist OR digital nerve of the index finger Stimulation intensity: sufficient to produce a minimal APB twitch OR at 2 to 3 times the sensory threshold Stimulation rate: 20 trials collected at 5- to 10-seconds interval Recording: surface EMG from bilateral upper limbs muscles (including APB, FDI and ADM)	/	0	/
Okuma et al., 2005	11 MSA-P (9), MSA-C (2)	Stimulation site: median nerve Stimulation rate: random rate of approximately 2 Hz Recording: surface EMGs from the forearm and hand muscles	40 (35–47)	7/11 (64%)	
Uozumi et al., 2008	12 PME (7), AD (2), CBS (2), EM (1)	Stimulation site: median nerve at rest and during muscle contraction Stimulus intensity and rate and width: not reported Recording: surface EMG from thenar muscles	41.8 (38.6–43)	12/12 (100%)	C-reflex recorded during voluntary contraction Cortical reflex myoclonus was classified into three subtypes: type I: C-reflex with recurrent C-reflex (C') type II: double C-reflexes (C 1, C2) type III: C-reflex with evident inhibition
Latorre et al., 2018	35 MSA (8), CBS (10), BAFME (4), celiac disease (3), mitochondrial disease (6), post anoxic (4)	NA	NA	10/18 (56%)	

AD: Alzheimer's disease, BAFME: Benign adult familial myoclonus epilepsy, CBS: cortico-basal syndrome, CJD: Creutzfeldt-Jakob disease, DCM: dyssynergia EM: essential myoclonus, HS: healhty subjects, MSA: multiple system atrophy, NA: not available, OPCA: olivopontocerebellar atrophy, PD: Parkinson's disease, PME: progressive myoclonic epilepsy, SSE: subacute spongiform encephalopathy.

time-locked to the event of interest (e.g., EMG activity responsible for the myoclonus) will survive the averaging process, while irrelevant activity will be cancelled out (Shibasaki and Kuroiwa, 1975).

Many patients have spontaneous or action-induced jerks that have no apparent sensory trigger. In such cases, a cortical origin can only be concluded if there is some evidence of EEG discharges time-locked to individual myoclonic jerks. A relationship between the spontaneously occurring myoclonus and EEG had previously been demonstrated without any forms of signal processing (Bradshaw, 1954, Dawson, 1946, Harriman et al., 1955, Kugelberg and Widen, 1954, Lance and Adams, 1963): when myoclonic jerks are generated by cortical activity, they are preceded by EEG discharges in the contralateral M1, occurring with a timing compatible with transmission along the corticospinal pathway. However, this relationship can be difficult to disclose. To overcome this, Shibasaki and Kuroiwa introduced the JLBA procedure in an attempt to demonstrate the EEG correlate of CM more efficiently. Since then, the method has been used in numerous studies (Table 3) to the point of being considered part of the "gold standard" evaluation of myoclonus (Hallett, 2018, Latorre et al., 2018a, Latorre et al., 2018b). Despite this, the JLBA is only positive in a limited number of clinically suspected CM (Latorre et al., 2018a). There might be several reasons for this, including the generally small sample size of the studies, and the fact that the patients included are affected by different diseases, which may show a variable link with CM.

4.1. The pathophysiology of EEG correlate of cortical myoclonus

Positive JLBA has been variably reported in progressive myoclonus epilepsy (Brown et al., 1999, Shibasaki et al., 1991, Shibasaki and Kuroiwa, 1975, Shibasaki et al., 1985b), benign adult familial myoclonus epilepsy (Guerrini et al., 2001), HD (Rossi Sebastiano et al., 2012), PD (Caviness et al., 2002), Lewy body dementia (Caviness et al., 2003) and multiple system atrophy (Okuma et al., 2005). CBS has been described as an exception among parkinsonisms, since myoclonus in this case is not preceded by definite EEG transients, but yet considered as cortical (Lu et al., 1998, Thompson et al., 1994b). This evidence considered, it is possible that myoclonus manifesting with similar clinical features can, in fact, have different pathophysiology. One important feature supporting this notion is the different latency between EEG and EMG discharges found in JLBA across different diseases. It is often assumed that the time between EMG discharges related to CM and the preceding EEG transient should be around 20 ms, compatible with transmission across fast corticospinal fibres (Shibasaki and Hallett, 2005, Shibasaki et al., 1978, Zutt et al., 2017, Zutt et al., 2018). However, longer latencies have been reported, for instance in Alzheimer's disease (Wilkins et al., 1984), coeliac disease (Brown et al., 1999), PD (Caviness et al., 2002), Lewy body dementia, Lennox-Gastaut syndrome (Wilkins et al., 1985) and, most notably, in Creutzfeldt-Jakob disease, where the time between EEG and EMG bursts can be several tens of ms (Shibasaki et al., 1981, Shibasaki et al., 1978). These data suggest that, at least in some diseases, the cortical activity responsible for clinically defined CM might be relayed to the spinal cord through slow-conducting descending pathways, such as those putatively implicated in other forms of involuntary muscle activity (Antelmi et al., 2018, Rothwell, 2006). It is more difficult to interpret reports where, by contrast, the latency between EEG and EMG bursts in JLBA is shorter than 15–20 ms (Brown et al., 1999, Caviness et al., 2002, Rossi Sebastiano et al., 2012, Sakai et al., 1993, Shibasaki et al., 1978, Shibasaki et al., 1985b, Wilkins et al., 1985), which is too brief to be compatible with transmission along even the fastest descending pathways. There might be technical reasons for this finding, including the difficulty in determining the latency from the EEG spike to the onset of myoclonus and the somewhat arbitrary nature of the threshold level for the trigger used in the JLBA (Brown et al., 1999, Carr, 2012, Guerrini et al., 2001, Sakai et al., 1993). However, another possibility, which has only seldom been suggested (Sakai et al., 1993), is that the EEG transient preceding myoclonus is subcortical in origin. This interpretation would be in keeping with the observation, reported in several studies where the time elapsing between EEG and EMG

Table 3
Summary of the studies considered where JLBA was performed.

Study	Disease	JLBA positive/total tested (%)	Time between EEG and EMG discharge (ms)
Shibasaki and Kuroiwa, 1975	Various	4/7 (57%)	10–100
Shibasaki et al., 1978	PME	7/14 (50%)	7–15
Shibasaki et al., 1978	SSE	2/2 (100%)	50–280
Hallett et al., 1977	CRM	3/3 (100%)	N/A
Shibasaki et al., 1981	CJD	2/2 (100%)	50–85
Rothwell et al., 1984	HT/unknown	3/3 (100%)	17–21
Wilkins et al., 1984	AD	7/10 (70%)	20–40
Wilkins et al., 1985	PGEM	11/11 (100%)	10–250
Shibasaki et al., 1985a, 1985b	PME	15/17 (88%)	6–22
Shibasaki et al., 1991	PME	5/5 (100%)	15–21.6
Sakai et al., 1993	Various	6/6 (100%)	13–16.4
Thompson et al., 1994a, 1994b, 1994c	CBD	4/14 (29%)	N/A
Lu et al., 1998	CBD	0/2	N/A
Brown et al., 1999	Various	3/8 (38%)	14–34
Salazar et al., 2000	pMSA	0/2	N/A
Guerrini et al., 2001	BAFME	10/10 (100%)	21
Caviness et al., 2002	PD	20/20 (100%)	15–40
Caviness et al., 2003	LBD	7/7 (100%)	23–30
Okuma et al., 2005	MSA	9/11 (82%)	20
Rossi Sebastiano et al., 2012	HD	3/3 (100%)	12–14
Zutt et al., 2017	Various	5/13 (39%)	N/A
Zutt et al., 2018	Various	5/9 (56%)	N/A

The time between EEG and EMG discharges refers to recording from hand muscles. AD: Alzheimer's disease; BAFME: Benign adult familial myoclonus epilepsy, CBD: corticobasal degeneration; CJD: Creutzfeldt-Jacob disease; CRM: cortical reflex myoclonus; LBD: Lewy body disease; HD: Huntington's disease; HT: head trauma; JLBA: jerk-locked back averaging, PGEM: primary generalized epileptic myoclonus; PME: progressive myoclonic epilepsy; pMSA: parkinsonian-type multiple system atrophy; SSE: subacute spongiform encephalopathy.

bursts was very short (Brown et al., 1999, Caviness et al., 2002, Shibasaki and Kuroiwa, 1975, Shibasaki et al., 1985b), that the EEG transient starts with a positive deflection; in this context, the latter might be interpreted as a far-field potentials generated subcortically, such as the P14 component of SEP (Erro et al., 2018, Rocchi et al., 2017). This issue is further complicated by the use of different reference electrodes (Brown et al., 1999, Caviness et al., 2002, Shibasaki and Kuroiwa, 1975, Shibasaki et al., 1985b), which makes it difficult to compare the phase of myoclonus-associated EEG transients.

4.2. JLBA and myoclonic jerks: Technical issues

There might be additional technical reasons that justify a negative JLBA in cases of clinically suggestive CM. For example, the recording of the JLBA can be difficult due to EEG artefacts and low frequency of the myoclonus (Zutt et al., 2017), or to high frequency and high-amplitude jerks (Shibasaki et al., 1978). However, these clarifications are not often reported, and it is not always clear if only a proportion of patients is investigated with JLBA because of technical difficulties or other factors. Other methodological issues which may contribute to the heterogeneity in results might be the number of trials used to obtain the JLBA (between 50 and 200), and the absence of specification of an EMG threshold, together with the fact that the latter is usually measured in a subjective way. It should also be noted that a possible lack of sensitivity to disclose pre-myoclonic cortical activity might be an intrinsic limitation of the EEG: at least one study, for instance, found that magnetoencephalography is more effective in isolating back-averaged cortical activity preceding myoclonus (Mima et al., 1998).

In conclusion, in the examined studies (summarised in Table 3), JLBA was able to confirm a clinical diagnosis of CM in about 70% of cases. Considering the presented evidence, demonstration of EEG transients in association with myoclonus usually suggests its cortical origin, but their absence does not exclude it.

5. Cortico-muscular connectivity

*Cortico-muscular connectivity refers to a series of measures designed to investigate functional linkage between brain and muscle, with the aim of providing information about neural drive to muscles (*Farmer et al., 1993, McLachlan and Leung, 1991*).*

Cortico-muscular connectivity measures, coherence in particular (CMC), have been used to investigate the relationship between voluntary or involuntary muscle contractions and cortical activity, with the assumption that high values of the metric used indicate a cortical drive to the observed EMG activity (Farmer et al., 1993, McLachlan and Leung, 1991). A few studies have investigated CMC in myoclonus (Brown et al., 1999, Grosse et al., 2003a, Grosse et al., 2003b, Guerrini et al., 2001, Panzica et al., 2014, Panzica et al., 2003, Panzica et al., 2010, Sharifi et al., 2021, Zutt et al., 2017, Zutt et al., 2018). In contrast to JLBA, CMC is not affected by the presence of high frequency myoclonic discharges and does not require the definition of an arbitrary trigger threshold (Avanzini et al., 2016, Shibasaki and Hallett, 2005). Thanks to these advantages, it is possible to measure CMC in patients with CM who have absent (Brown et al., 1999) or inconsistent (Grosse et al., 2003a) JLBA, and in particular in those with high-frequency myoclonus. On the other hand, assessing CMC is technically difficult and requires artefact-free EEG epochs (Grosse et al., 2003a). So far, the information provided by CMC has been limited; this may depend on methodological factors including small sample sizes (usually in the range of 6–13), heterogeneous patient populations, or weakness of results on an individual basis (Grosse et al., 2003a).

5.1. CMC and myoclonic jerks: Technical issues

Possible technical sources of variability include the approach used to perform frequency decomposition before estimating CMC. A limitation to the commonly used Fourier transform is that a high frequency resolution can be reached only if long time windows are used (Brown et al., 1999), thus increasing the risk of spurious results due to signal non-stationarities. Univariate (Panzica et al., 2003) and multivariate autoregressive models have been used to measure CMC in myoclonus. These approaches yield a frequency resolution, even when applied to short epochs, and do not require any averaging to obtain a smooth power spectrum (Panzica et al., 2003, Panzica et al., 2010).

5.2. Pathophysiology of CMC

While there is general agreement on the finding of higher CMC in patients with CM than healthy controls, particularly in the beta band, there is high variability in regards to the frequency bands involved, which vary between 6 Hz (Grosse et al., 2003a, Grosse et al., 2003b, Guerrini et al., 2001) and 175 Hz (Brown et al., 1999). One reason for this variability might be that different diseases presenting with CM are associated with different CMC features. For instance, CMC in the alpha band was found in patients with Unverricht–Lundborg disease, while sialidosis was associated with significant CMC in the gamma band and in severe cases of Lewy body dementia the CMC had a more complex profile, with multiple peaks (Panzica et al., 2003). By contrast, no significant EEG-EMG coherence was found in patients affected by CBS, while significant intermuscular coherence in the beta band was noted, perhaps suggesting a subcortical origin of the myoclonus. Overall, these findings might indicate that CMC has disease-specific characteristics in patients with myoclonus, possibly reflecting the activity of different cortical and subcortical multidirectional components.

An intrinsic limitation to coherence is that it does not give directional information about connectivity (Rossini et al., 2019). Whether a signal source is driving another can be inferred with alternative methods, one of which is the calculation of phase lag. By using this technique, several studies suggested that, in CM, activity in M1 drives muscle discharges in contralateral muscles, with a latency often compatible with transmission along the corticospinal pathway (Grosse et al., 2003a, Guerrini et al., 2001, Panzica et al., 2014, Panzica et al., 2003). However, a considerable variability in this latency has been reported (Grosse et al., 2003a, Guerrini et al., 2001, Panzica et al., 2014, Panzica et al., 2003) (8–21 ms), with low values too. This finding, similar to that reported previously for JLBA (Brown et al., 1999, Caviness et al., 2002, Rossi Sebastiano et al., 2012, Sakai et al., 1993, Shibasaki et al., 1978, Shibasaki et al., 1985b, Wilkins et al., 1985), might suggest a possible subcortical origin of the myoclonus or point to technical factors which might limit the reliability of the estimation of cortico-muscular transmission time by phase lag measurement, such as the use of interference EMG (Ibanez et al., 2021). Another method used to disclose directional features of cortico-muscular connectivity in CM is partial directed coherence, which has demonstrated significant cortico-muscular drive in the beta band in patients with Unverricht–Lundborg disease (Panzica et al., 2014) and benign adult familial myoclonus epilepsy (Sharifi et al., 2021). However, significant values were also obtained from the hemisphere ipsilateral to muscles showing myoclonus (Panzica et al., 2014), while in some cases evidence for afferent flow of information, from muscles to the contralateral cortex, has been found (Panzica et al., 2014, Sharifi et al., 2021).

In the examined studies (summarised in Table 4), high CMC (mostly at the beta and gamma frequency band) was found in about 85% of the cases. Overall, while cortico-muscular connectiv-

Table 4
Summary of the studies considered where CMC was performed.

Study	Disease	CMC positive/total tested (%)	Frequency band
Brown et al., 1999	Various	8/8 (100%)	2 at < 10 Hz 6 at 15–30 Hz 6 at 30–60 Hz 4 at 60–90 Hz 3 at > 90 Hz
Guerrini et al., 2001	BAFME	5/7 (71%)	8–25 Hz
Grosse et al., 2003a	CBD	1/5 (20%)	~10 Hz
Grosse et al., 2003b	Various	No data at individual level	~15 Hz
Panzica et al., 2003	PME	15/15 (100%)	13–26 Hz
Panzica et al., 2010	PME (ULD and SIAL)	9/9 ULD 3/3 SIAL (100%)	16–25 Hz
Panzica et al., 2014	ULD	13/13 (100%)	20 Hz
Zutt et al., 2017	Various	4/8 (50%)	NA
Zutt et al., 2018	Various	16/20 (80%)	Alpha and beta band
Sharifi et al., 2021	BAFME	7/7 (100%)	12–25 Hz

BAFME: benign adult familial myoclonus epilepsy, CBD: corticobasal degeneration, CMC: corticomuscular coherence, PME: progressive myoclonic epilepsy, SIAL: sialidosis, ULD: Unverricht–Lundborg disease.

ity assessment has disclosed meaningful information in the context of CM, further studies are needed to assess its disease-specificity, as well as its ability to provide causal information about cortico-muscular dynamics.

6. Transcranial magnetic stimulation

Although transcranial magnetic stimulation (TMS) is not routinely used for the diagnosis of CM, it has been applied to test M1 net excitability, as well as facilitatory and inhibitory intracortical circuits (Spampinato et al., 2023), in patients with CM. Unlike the neurophysiological techniques mentioned above, TMS studies have not identified potential neurophysiological correlates of CM but have provided evidence on the pathophysiology of neurological conditions that include CM (Nardone et al., 2018).

A number of single- and paired-pulse TMS paradigms have been used to investigate M1 in patients with CM. For instance, by using single-pulse TMS, independent groups investigated resting motor threshold (RMT), which was found to be normal in juvenile myoclonus epilepsy (Manganotti et al., 2006, Manganotti et al., 2000, Manganotti et al., 2004), reduced in familial cortical myoclonus with epilepsy (Dubbioso et al., 2022, Guerrini et al., 2001, Suppa et al., 2009, van Rootselaar et al., 2007) and increased in progressive myoclonus epilepsy type 1 (EPM1, Unverricht-Lundborg disease) (Danner et al., 2009, Danner et al., 2011, Hypponen et al., 2015). This variability of results is present also in other single- and paired-pulse TMS measures tested in patients with neurological diseases associated with CM (Nardone et al., 2018); this suggests that abnormalities of these parameters are more likely to be disease-specific rather than associated with CM itself. A relevant exception to this scenario is represented by the short-interval intracortical inhibition (SICI). SICI is obtained by conditioning a test motor evoked potential with a subthreshold TMS applied 1–6 ms before and is thought to reflect the activity of GABA-ergic intracortical interneurons (Fong et al., 2021, Kujirai et al., 1993). A solid body of evidence suggests that SICI is impaired in patients with CM, regardless of its etiology (Brown et al., 1996, Caramia et al., 1996, Hanajima et al., 1996, Inghilleri et al., 1998, Manganotti et al., 2006, Manganotti et al., 2000, Manganotti et al., 2004, Manganotti et al., 2001, Suppa et al., 2009, van Rootselaar et al., 2007). In addition, a recent study demonstrated that SICI impairment correlates with the number of repeat expansions in the more affected allele in patients with progressive myoclonus epilepsy type 1 (Silvennoinen et al., 2023). Overall, these findings support the notion that a defective cortical GABA-A-mediated inhibition may play a key role in the genesis of CM, independently from the underlying neurological disease.

7. EMG burst duration

A brief duration EMG burst is usually considered a supportive criterion for the diagnosis of CM (Shibasaki and Hallett, 2005). Wilkins and colleagues were the first to state that, in their investigation of patients with "primary generalized epileptic myoclonus", burst durations were uniformly 10–50 ms (Wilkins et al., 1985). A similar, short duration (25–50 ms) was found in multiple system atrophy (Thompson et al., 1994b). This notion was generalized by Tassinari and colleagues, who stated that in CM the duration of the discharge is less than 50 ms (Tassinari et al., 1998). There is some variability in the duration of EMG bursts reported in the literature, but there is good agreement on figures ranging from 10 to 100 ms, regardless of the etiology of the CM (Caviness, 2009, Caviness et al., 2002, Caviness et al., 2003, Guerrini et al., 2001, Okuma et al., 2005, Rossi Sebastiano et al., 2012, Salazar et al., 2000, Zutt et al., 2017, Zutt et al., 2018). However, this range of durations seems to be based on a qualitative description of EMG bursts, rather than a quantitative analysis, since details on the number of bursts considered and on measurement of amplitude threshold or burst duration are not reported. Although the short duration of bursts can coincide in most cases with a clinical suspicion of CM (Latorre et al., 2018a), its specificity with respect to other movement disorders has not been thoroughly investigated. In fact, it is known that fasciculation potentials can be shorter than 50 ms (Mills, 2010) and that spinal myoclonus can be associated with short-lasting EMG discharges too (Shibasaki, 2006). It is also important to note that discriminating between EMG discharges related to CM and voluntary activity may not be straightforward. In fact, activation of a single motor unit, with consequent EMG bursts of very short duration, has been demonstrated to be possible in healthy subjects, for instance during brief ballistic movements (Collins et al., 2020) or slight steady muscle contraction (Fournier et al., 1986, Marchand-Pauvert et al., 2000). Although these data demonstrate that EMG bursts of short duration are not inevitably pathological, other data suggests that they are not necessarily generated in the cortex (Mills, 2010, Shibasaki, 2006). Finally, the procedure to measure EMG burst duration is not defined and automated quantification of bursts length would be useful to draw more definite conclusion about EMG bursts features in CM.

8. Positive and negative myoclonus

It has been suggested that negative and positive myoclonus often coexist more frequently in CM than in other myoclonus subtypes (Avanzini et al., 2016, Cassim and Houdayer, 2006, Kojovic et al., 2011, Shibasaki, 1995, Shibasaki and Hallett, 2005, Tassinari et al., 1998). However, there is no clear evidence to confirm this. A few studies mention the co-occurrence of positive and myoclonus jerks and use it as a supporting feature of the cortical origin of the jerks (Koens et al., 2016, Latorre et al., 2018a, Zutt et al., 2017, Zutt et al., 2018); however, none of these has thoroughly compared this feature among the different forms of myoclonus.

9. Craniocaudal progression of the jerks

Proximal to distal, or craniocaudal, propagation of the myoclonic jerks, compatible with conduction in the fast-conducting component of the corticospinal tract, has been described in a few studies of CM and proposed as a potential and useful pointer to suggest cortical involvement (Hainque et al., 2018, Kojovic et al., 2011, Latorre et al., 2018a, Shibasaki and Hallett, 2005, Thompson et al., 1994c). Nevertheless, the evidence supporting this notion is not clear, although a paper of Brown and colleagues (Brown et al., 1991) has been often cited for this purpose. In this paper, the authors investigated the intra and interhemispheric spread of myoclonic activity in patients with CM and noticed that the myoclonic activity spreads along the somatotopic body map of the sensorimotor cortex. The authors observed that the difference in reflex myoclonus latency induced by electrical median stimulation and following magnetic stimulation of the motor cortex was longer than expected. The delay was attributed to the interhemispheric spread of activity, that grossly followed the sensorimotor cortex somatotopic pattern; although a spread occurring within a subcortical structure with somatotopic arrangement before reaching the cortex could not be excluded (Brown et al., 1991). This observation does not imply that a craniocaudal pattern of muscle activation in myoclonus is suggestive of a cortical origin of the jerks.

10. Discussion

Based on our review, the evidence to support the electrophysiological criteria of CM does not appear to be very solid. This is due to a combination of factors, including biased study designs, technical issues and the small amount of data available, which is at odds with the strong belief of the robustness of these criteria.

Overall, the criteria have been demonstrated in relatively small number of patients suspected to have CM; nevertheless, it is difficult to acknowledge if this is because of an intrinsic limitation of the techniques in demonstrating the cortical origin of myoclonus, or due to low clinical-electrophysiological agreement. This uncertainty is due to the lack of a gold standard, which is required to define the specificity and sensitivity of a measure and that is difficult to determine in this case. This may be a consequence of the clinical overlap among myoclonus subtypes and the lack of disease/myoclonus-specific electrophysiological features, as shown above.

It is evident from the review that no single criterion can be used to support a definitive diagnosis of CM. Even tests that are often considered as irrefutable proof of cortical origin, such as positive JLBA or short duration myoclonic bursts, are not infallible. One way around the problem might be to tighten the criteria. For example, JLBA could require that the interval between the onset of EEG and EMG activity is within a few milliseconds of the patient's own corticospinal conduction time. Patients in whom the interval was shorter would have to be excluded because it could be that their myoclonus originates subcortically, although this would also exclude patients with true CM in whom the EEG failed to detect the onset (or even occurrence) of cortical activity. Conversely, the jerks of patients in whom the interval was too long could arise subcortically and use a slow conducting reticulospinal pathway to produce myoclonus. Nevertheless, this would exclude CM patients in whom cortical activity had to build to a threshold value before provoking a corticospinal volley.

A practical approach to deal with these problems is to acknowledge the uncertainties of existing criteria and combine data from multiple investigations. Thus, although a patient who fulfils very tightly defined criteria for JLBA is highly likely to have CM, patients who are positive for JLBA but outside the strict criteria may still have CM if supported by additional data, such as the presence of a giant SEP. Many investigators implicitly adopt this approach: our argument here is that we need to acknowledge this more openly and propose a formal classification of CM in terms of levels of evidence. Table 5 summarises the levels of certainty provided by different techniques, which might be the starting point to guide further research to develop clearer definitions of existing criteria. We need a more precise definition of giant SEP and EMG threshold for back averaging, and automated process for EMG burst detection. Furthermore, the criteria should be tested in larger populations of CM and other myoclonus syndromes, and healthy controls, to determine their diagnostic accuracy; and other techniques, such as TMS, might be explored for their potential diagnostic utility. Finally, it is important to consider that the contribution of sensorimotor cortices can be variable in CM origin, with motor and sensory cortex involvement being prevalent in most of the patients, while in a minority motor or sensory cortex might be implicated alone, giving different electrophysiological findings as suggested by previous studies (Mochizuki et al., 1999, Terao et al., 1997, Uesaka et al., 1993, Ugawa et al., 2002); we should also recognise that myoclonus may be generated by a network involving cortical and subcortical structures, and that "pure" CM may be observed only in few selected cases.

Table 5
Reliability of neurophysiological criteria of cortical myoclonus.

Technique	Comment
JLBA	Highly supportive of cortical origin if latency between EEG and EMG bursts is about 20 ms
Giant SEP*	Not specific for CM, but indicative of S1 hyperexcitability
C-reflex	Requires a more specific definition, reliability not known
CMC	Proves cortico-muscular connectivity, but not directional or causal interaction. Reliability not known
Short EMG burst duration	Not specific for CM, reliability not known
Positive and negative jerks	Reliability not known
Craniocaudal progression	Not specific for CM, reliability not known

CM: cortical myoclonus, CMC: cortico-muscular coherence, EEG: electroencephalography, EMG: electromyography, JLBA: jerk-lock back averaging, SEP: somatosensory evoked potentials.

* Threshold amplitude for the definition of giant to be determined and subject to clinicians' judgement until further studies are performed.

In conclusion, although the electrophysiological criteria for the diagnosis of CM may be useful if properly used, we believe that they should be reviewed. We propose that combining more than one tests, together with the clinical features, is very likely the best approach to increase the diagnostic accuracy at present. Nevertheless, larger studies are needed to standardise the methods, to resolve methodological issues, to establish the diagnostic criteria sensitivity and specificity and to develop further methods that might be useful to clarify the pathophysiology of myoclonus.

Declaration of Interest

None.

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