EDUCATIONAL OBJECTIVES
Myoclonus is one of the most frequently encountered involuntary movements in clinical neurology, but its pathophysiologic mechanisms have not been fully understood. After completion, the reader should be able to compare the currently available electrophysiologic techniques for clinically investigating myoclonus.

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Electrophysiological Studies of Myoclonus

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Myoclonus, one of the most commonly encountered involuntary movements, is characterized by sudden, brief, jerky, shock-like movements involving the extremities, face, and trunk, without loss of consciousness. Most myoclonic jerks are caused by abrupt muscle contraction (positive myoclonus), but similar jerks are sometimes caused by sudden cessation of muscle contraction associated with a silent period in the ongoing electromyographic (EMG) activity (negative myoclonus) (Fig. 1). The term myoclonus is derived from the original report by Friedreich, who in 1881 reported a 50-year-old man manifesting involuntary small muscle jerks mostly at rest, and called it “paramyoclonus multiplex.” In 1988, Shibasaki reviewed electrophysiological studies of myoclonus in a minimonograph for the American Association of Electromyography and Electrodiagnosis, and this was revised in 2000. In view of the rapid advance in understanding of the pathophysiology of myoclonus, especially owing to the clinical application of transcranial magnetic stimulation (TMS), it was decided to update the monograph again. Since most myoclonic jerks are not pathognomonic of any particular disease, this monograph discusses the pathophysiological issues relating to myoclonus in general, but not each individual disease causing myoclonus.

CLASSIFICATION OF MYOCLONUS

Myoclonus can be classified into three groups (cortical, subcortical, and spinal myoclonus) based on the presumed physiological mechanism underlying its generation. Cortical myoclonus is further classified into three subtypes: spontaneous cortical myoclonus, cortical reflex myoclonus, and epilepsy partialis continua (EPC). If EPC is defined as “continuous muscle jerks of focal cortical origin,” this phenomenon is seen in diverse conditions and is associated with generalized convulsions in many cases. In this group, however, there is a unique condition characterized by continuous focal muscle jerks not associated with generalized convulsions, and in this regard it is distinct from just a focal form of spontaneous or reflex cortical myoclonus. In view of the fact that spontaneous or reflex cortical myoclonus also shares some common features with epilepsy, the terminology of EPC for this particular
condition will be used instead of proposing a new terminology.

Most myoclonic jerks of cortical origin are stimulus sensitive, being elicited by stimuli of a single or multiple modalities, and are thus called cortical reflex myoclonus. Most patients presenting with cortical myoclonus have both positive and negative myoclonus which occur either independently of each other or together as a complex of the two kinds of myoclonus (Fig. 1). Cortical myoclonus is not disease-specific.  

Subcortical myoclonus includes essential myoclonus, periodic myoclonus, dystonic myoclonus, reticular reflex myoclonus, startle syndrome, and palatal tremor. Essential myoclonus is a nonprogressive disorder not associated with any seizures or other neurological deficits, and probably includes several subtypes hitherto unclassified. Essential myoclonus usually occurs irregularly and is not stimulus sensitive. There have been a few reports of familial essential myoclonus. Periodic myoclonus is seen typically in patients with CJD, usually in association with periodic synchronous discharges (PSDs) on electroencephalogram (EEG). Subacute sclerosing panencephalitis (SSPE) is also characterized by periodic movement, but in this condition the movement is associated with a much slower muscle contraction resembling dystonia rather than a myoclonic jerk. Palatal tremor corresponds to an involuntary vertical oscillation of the soft palate, previously called palatal myoclonus. Myoclonus of spinal cord origin (spinal myoclonus) occurs either irregularly or quasi-periodically, and it can be repetitive at a rapid rate (rhythmic spinal myoclonus). Spinal myoclonus of slowly repetitive (periodic) form may be stimulus sensitive. It tends to involve a group of muscles innervated by a certain spinal segment (segmental myoclonus). Spinal myoclonus sometimes arises from a certain spinal segment and slowly spreads rostrally as well as caudally, probably being conducted through the proprio-spinal tract (propriospinal myoclonus).

Clinical features of each group of myoclonus are summarized in Table 1. This classification is important especially from the viewpoint of treatment, because, regardless of the underlying diseases or etiologies, cortical myoclonus is usually more severe than myoclonus of other categories, and patients with cortical myoclonus often develop generalized convulsive seizures.

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological studies are useful in the evaluation of myoclonus, not only for confirming the
clinical diagnosis but also for understanding the underlying physiological mechanisms. Since the majority of myoclonic jerks are believed to be caused by hyperexcitability of a group of neurons in certain cerebral structures, the relationship of myoclonic jerks with EEG activity is of primary importance in the study of myoclonus. Since 1938 when Grinker et al. first reported a short train of EEG spikes associated with myoclonic jerks in two patients with familial myoclonus epilepsy, polygraphic recordings of EEG and EMG by using either an electroencephalograph or cathode ray oscilloscope have been widely employed. Since 1975, backward averaging of EEG time-locked to the myoclonic EMG discharge (jerk-locked back averaging) has been used and found effective for detecting EEG correlates of myoclonus that are otherwise unrecognizable, and also for investigating the temporal and spatial relationship between myoclonus and EEG activities. Negative myoclonus of cortical origin also can be studied by the same principle. Namely, the onset of negative myoclonus can be detected as a sudden cessation of EMG discharge (the beginning of the silent period) or by the aid of accelerometer, which is then used as a fiducial point for back averaging the simultaneously recorded EEG (silent period-locked back averaging). More recently, clinical application of magnetoencephalogram (MEG) has enabled us to investigate the cortical mechanisms involved in myoclonus generation with relatively higher spatial resolution than EEG, These previous studies have analyzed the electrical or magnetic fields of cortical potentials time-locked to muscle jerks. By contrast, Brown and colleagues applied the technique for analyzing the correlation of rhythmic oscillations of cortical activities with those of EMG discharges (cortico-muscular coherence) to the study of myoclonus.

Since Dawson, in 1946, found an exaggerated EEG response to electrical shocks delivered to the peripheral nerve in a patient with myoclonic epilepsy, somatosensory evoked potentials (SEPs) have been widely used for the study of myoclonus, and in particular for stimulus-sensitive myoclonus. The reflex jerk can often be recognized in the surface EMG as an enhanced, long-latency reflex in response to the stimulus, referred to as a C reflex. In cortical reflex myoclonus, the enhanced EMG response is mediated by a transcortical reflex pathway; other “long loops” are possible in other types of myoclonus.

The role of the cerebral cortex in the pathogenesis of myoclonus can be further investigated by studying the cortical excitability change immediately after a spontaneous myoclonus by employing the technique of jerk-locked evoked potentials and by comparing its results with the recovery function of evoked responses obtained by using a paired stimulation paradigm at variable interstimulus intervals (ISIs). The clinical application of TMS has allowed the excitability changes of the motor cortex to be studied in patients with myoclonus by stimulating the cortex more directly than by previous methods. This technique, however, should be applied with great caution, especially in patients with cortical myoclonus, in order to avoid causing a generalized convulsion.

Electrophysiological techniques currently available to study myoclonus are listed in Table 2, along with the main implication of each method.

### EMG CORRELATES OF MYOCLONUS

Most myoclonic jerks can be easily diagnosed based on clinical observation, but some are difficult to distinguish from other involuntary movements such as tremor, chorea, and dystonia. In this situation, recording EMG discharges associated with involuntary movements using surface electrodes is extremely helpful, because one of the most important characteristics of myoclonus is an abrupt and brief muscle contraction. For this purpose, EMGs are recorded by placing a pair of disc or cup electrodes about 3 cm apart on the skin overlying each muscle. In a small muscle like adductor pollicis brevis, only one electrode can be placed over the muscle while another

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*Periodic, slowly repetitive with clearly recognizable intervals between successive jerks; rhythmic, fast repetitive without clearly recognizable intervals between successive jerks.

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Table 2. Electrophysiological studies of myoclonus.

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EEG, electroencephalogram; EMG, electromyogram; MEG, magnetoencephalogram.

electrode is placed over a tendon. It is extremely important to discover by clinical observation the most active muscles from which the myoclonic jerk of interest can be recorded. The bandpass filter for EMG recording can be set to, for example, 50–1,000 Hz. The use of a relatively high low-frequency filter, corresponding to a time constant of 0.003 s, is for excluding movement artifacts, most of which are in the low frequency range. It is useful to record EMGs simultaneously from multiple muscles, if possible, not only to demonstrate the distribution and spread of myoclonic jerks, but also to discover the best muscle for subsequent analysis, especially for the purpose of the jerk-locked back averaging.

Myoclonic jerks of cortical origin are characterized by an extremely short duration of the EMG correlates, usually less than 50 ms (Fig. 2), whereas those of subcortical origin (except reticular reflex myoclonus) have EMG correlates of much longer duration. Cortical myoclonus, with the exception of EPC, involves a variety of muscles, either independently or concurrently, and commonly involves agonist and antagonist muscles synchronously. In some cases, multichannel EMG recording from an extremity can demonstrate spread of jerks from the proximal to the distal muscles with the conduction velocity approximately corresponding to that of alpha motor fibers5 (Fig. 3). Cortical myoclonus usually occurs irregularly, but infrequently it appears to be rhythmic,7 especially in patients with familial cortical myoclonic tremor,79 which was also reported by the name of BAFME,95 cortical tremor,34,82 or familial cortical tremor with epilepsy,56 and in those with CBD.9,12,44,77,81 When myoclonus consists of frequent, independent contraction of multiple small muscles of distal limbs, it is called minipolymyoclonus.89 Cortical myoclonus is usually stimulus sensitive, being elicited most commonly by tendon tap, posturing, and passive or volitional movement, and can also be elicited by emotional excitation.

Negative myoclonus can also be identified clinically without difficulty if special attention is paid to its possibility, but as with positive myoclonus, the recording of its EMG correlates confirms the clinical impression. For this purpose, it is always important to record EMGs not only in the resting condition but also during isometric contraction of the corresponding muscles, most commonly from wrist extensor muscles while the wrists are maintained in extended position. In fact, even in a single patient, both positive and negative myoclonus can be seen in various proportions, either independently or in combination (Fig. 1). When both forms of myoclonus occur in combination, the abrupt increase in muscle discharge (positive myoclonus) often precedes the onset of the silent period (negative myoclonus), but occasionally follows its offset.

In CJD, myoclonus is usually not stimulus sensitive and occurs continuously and quasi-periodically in the resting condition with time intervals ranging from 600–1,500 ms. It is often overlaid on a dystonic posture or associated with dystonic movement of the corresponding extremity. The duration of each myoclonic EMG discharge is usually longer than that of cortical myoclonus, but it can be as short as in cortical myoclonus. The EMG discharges recorded from the same muscle may vary considerably in duration among movements. Patients with CJD may also show typical cortical reflex myoclonus in advanced stages of the disease when PSDs tend to disappear and the background EEG activity becomes very low in amplitude.72 In this case, myoclonus is often elicited not just by somatosensory stimulation but also by photic stimulation.72

Involuntary movements seen in patients with SSPE are associated with an EMG discharge of stereotyped waveform and long duration, resembling dystonia, and occur periodically with regular intervals of 4–13 s.

Essential myoclonus is associated with EMG discharge of relatively long duration. Dystonic myoclonus, by definition, is characterized by EMG discharge of much longer duration than cortical myoclonus.
Whether palatal or oculopalatal myoclonus belongs to myoclonus in the narrow sense has long been controversial. The term “palatal tremor” is used more often instead, because the movement in this condition is rhythmic and associated with an EMG discharge of as long as 400 ms, and hence does not appear shock-like. Palatal tremor is classified into essential and symptomatic groups. Symptomatic palatal tremor is caused by various lesions affecting the Guillain–Mollaret triangle in the brainstem or cerebellum, and is often associated with vertical ocular movements or rhythmic limb movements, which appear to be a rhythmic oscillation rather than periodic movements. This involuntary movement continues rhythmically at a rate of 60–180/min, and the symptomatic form is uninterrupted during sleep whereas the essential form disappears during sleep. In essential palatal tremor, the involved muscle is the tensor veli palatini, whereas in symptomatic palatal tremor, it is the levator palatini. Therefore, the patient with essential palatal tremor often complains of ear clicks.

Recording EMG from multiple muscles is also useful in the study of spinal myoclonus. Segmental spinal myoclonus is characterized by simultaneous occurrence of myoclonic jerks in a group of muscles innervated by a certain spinal segment. Propriospi- nal myoclonus shows spread of myoclonic jerks from

**Figure 2.** Electroencephalogram–electromyogram (EEG–EMG) polygraphic records in a patient with progressive myoclonus epilepsy (PME) manifesting positive myoclonus in the hands at rest. Note that most myoclonic jerks are associated with a spike-and-wave complex on EEG. EEG recorded in reference to ipsilateral earlobe electrode, and negativity shown upward. ECR, extensor carpi radialis muscle; 1st DI, first dorsal interosseous muscle; Rt, right.
a certain spinal segment to rostral as well as caudal segments with a relatively slow speed of approximately 10 m/s.

EEG CORRELATES OF MYOClonUS

Simultaneous recording of EEG and EMG is basic yet important for the clinical study of any kind of myoclonus. This simple study serves as a guide to subsequent investigations by providing useful information in terms of the approximate relationship between the myoclonus and EEG activities. Recording of the EEG–EMG polygraph before carrying out more sophisticated investigations is most effective and time-saving, because the polygraph reveals which muscles are most commonly involved by the myoclonic jerks of interest.

The EEG can be recorded from electrodes placed mainly over the central areas, using either a bipolar or referential derivation with earlobe reference. The band pass setting may be the same as the one used for recording the conventional EEG (e.g., 0.5–500 Hz). The low-frequency (high-pass) filter of this setting corresponds to a time constant of 0.3 s. Since most myoclonic jerks of cortical origin are derived from the sensorimotor cortex, the central region should be covered by at least three electrodes, including C3, Cz, and C4 of the International 10-20 System. It is more efficient to record from multiple electrodes simultaneously (as far as the equipment allows) because this provides better spatial information and helps in distinguishing artifacts such as eye blinks, EMG, and body movements. Digital EEG equipment is extremely useful for this kind of polygraphic recording because it allows off-line analysis of the stored data after the actual recording by modifying various recording conditions such as electrode montage, paper speed, and filter setting as necessary.

In cortical myoclonus, the EEG usually shows multifocal or generalized spike-and-wave or multiple spike-and-wave discharges with or without associated myoclonus (Fig. 2). On the conventional polygraph, however, the temporal and spatial relationship between myoclonus and its EEG correlate is often difficult to determine quantitatively.

Negative myoclonus of cortical origin may also be associated with an EEG spike or spike-and-wave complex (Fig. 4). Again, however, it is difficult to determine precisely the temporal and spatial relationship between myoclonus and its EEG correlate is often difficult to determine quantitatively.

Negative myoclonus of cortical origin may also be associated with an EEG spike or spike-and-wave complex (Fig. 4). Again, however, it is difficult to determine precisely the temporal and spatial relationship between myoclonus and the associated EEG spike on the conventional polygraph. Furthermore, since the silent period tends to be preceded or followed by an abrupt EMG discharge (positive myoclonus), it is often difficult to judge whether the detected EEG spike is directly related to the positive or negative component of the EMG discharge.

In CJD, the periodic myoclonus is frequently associated with PSDs in the EEG with somatotopic relationship of various degrees between the two phenomena. These two phenomena may appear synchronously, but in some cases or at a certain stage of the disease in individual cases, either periodic myoclonus or PSD alone may be seen; even when
they appear concurrently, there may be a significant amount of jitter between the onset of the EMG discharge and that of the PSD. In SSPE, the involuntary movement is constantly associated with periodic, high-amplitude EEG discharges of stereotyped waveform. In this condition, the temporal and spatial relationship between the central and peripheral activities is quite constant among the periodic phenomena in each individual case.55

Essential myoclonus and dystonic myoclonus are not associated with any EEG abnormality. Patients with palatal tremor do not show any EEG abnormality, unless accompanied by other cerebral diseases.

JERK-LOCKED BACK AVERAGING

Jerk-locked back averaging is essentially an extension of the EEG–EMG polygraph, and its principle is to back average the simultaneously recorded EEGs with respect to myoclonus. Recording can be done with the patient placed either in the sitting, reclining, or supine position, depending on the patient’s condition. Surface EMGs are recorded by using exactly the same method as used for recording with the EEG–EMG polygraph. The filter setting of 50–1,000 Hz can be used. The amplified EMG is preferably rectified or rectified and integrated to obtain a trigger pulse, but the onset of the amplified EMG itself (raw data) may be also used. In the case of negative myoclonus, the movement may be monitored by an accelerometer, so that the onset of its signal can be used as a fiducial point for averaging (Fig. 4).63,86

The recording of EEGs for the purpose of jerk-locked back averaging is also based on the conventional EEG–EMG polygraph. When jerks are recorded from an upper extremity, electrodes should be placed at least over the hand motor-area on each hemisphere. A point 2 cm in front of the somatosensory hand area is used as the hand motor-area, which for practical purposes can be substituted by C3 and C4 of the International 10-20 System. Likewise, the vertex electrode (Cz) is used for studying myoclonus of a lower extremity. It is useful to record from the Cz electrode regardless of the site of EMG recording, because the midline vertex serves as an important landmark for studying the scalp distribution of the myoclonus-related EEG activity. Additional electrodes may be applied depending on the location of the jerks. The electrode impedance should be kept below 5 kohm. Either common referential derivations with reference to the earlobe electrode or bipolar derivations, or both, can be adopted. The bandpass filter may be set to 0.5–1,000 Hz.

The analysis window may be freely determined depending on the purpose of the study, but usually it is set to 200 ms before and 200 ms after the myoclonus onset. The number of sweeps is again flexible,
but 50 sweeps per session are usually sufficient to demonstrate the myoclonus-related EEG activity, if there is any. Just like conventional evoked potentials, it is recommended to confirm the reproducibility of the results by repeating the session at least twice for each muscle. When the high-frequency filter is set to 1,000 Hz, a minimal sampling rate of 2,000 Hz is required for analog-to-digital conversion.

In spontaneous cortical myoclonus or cortical reflex myoclonus, this technique can disclose a myoclonus-related EEG activity that may not be recognizable on the conventional polygraph. More commonly, this technique is used to study the precise interval from the EEG activity to the myoclonus as well as to study the scalp distribution of the myoclonus-related EEG activity based on simultaneous multichannel recordings. Epilepsia partialis continua is a good clinical indication for applying this technique.

In myoclonus of cortical origin, the jerk-locked back averaging technique commonly discloses a positive–negative, biphasic spike at the central electrodes somatotopically corresponding to the muscle from which the myoclonus is recorded. The initial positive peak of the EEG spike precedes the onset of myoclonic EMG discharge of a hand muscle by approximately 20 ms. The more distal the muscle from which the myoclonus is recorded, the longer is the EEG–EMG time interval, and vice versa. The widespread distribution of the myoclonus-related EEG activity, as seen in Figure 3, may be related, at least partially, to the involvement of multiple muscles by the myoclonus with a short time delay. In this regard, Brown and colleagues postulated, based on clinical electrophysiological studies, that the myoclonus-related cortical discharge may spread through the motor cortex within one hemisphere as well as to the homologous area of the contralateral motor cortex transcallosally.

Another cause of the widespread distribution of the myoclonus-related EEG activity is, as with any other high-voltage EEG activity, the shunt effect due to different electrical conductivity of the tissues covering the cerebral cortex, such as spinal fluid and skull. In this respect, since magnetic fields generated from the cerebral cortex theoretically are not influenced by those surrounding structures, MEG often enables the source of the myoclonus-related cortical activities to be investigated more easily and more accurately than EEG. Uesaka and colleagues studied seven patients with cortical reflex myoclonus including one with EPC by using an MEG system equipped with 37 channel axial gradiometers, and showed that the cortical activity preceding myoclonus was localized in the postcentral gyrus in five patients; exceptions were a patient with EPC who showed the source in the precentral gyrus and another patient with cortical reflex myoclonus who showed two sources, one in the precentral and the other in the postcentral gyrus. Mima and colleagues studied six patients with cortical myoclonus by applying the technique of jerk-locked back averaging to the magnetic fields which were recorded by using a whole-head MEG system with planar gradiometers, and also to the simultaneously recorded EEGs. They detected the pre-myoclonus cortical activity on MEG in all cases (Fig. 5).
in two cases including a case of corticobasal degeneration, the myoclonus-related activity was detected only on the back-averaged MEG, and not on the EEG. They further identified the equivalent current dipole (ECD) for the myoclonus-related activity in the precentral gyrus in all cases. The discrepant results between these studies\textsuperscript{47,83} might be due to the different gradiometers used (axial vs. planar), different methods of data analysis, and different populations of patients. As Mima and colleagues\textsuperscript{47} recorded MEG and EEG simultaneously, and thus could correlate the averaged waveforms between the two, and as they could estimate the direction of intracellular current flow in the apical dendrite of pyramidal neurons for each dipole source, it is reasonable to postulate based on their data that cortical myoclonus in most cases is generated in the primary motor cortex.

Theoretically, MEG can record only the current flow which is oriented tangentially with respect to the head surface, whereas EEG can record both the tangentially and radially oriented current sources. However, MEG allows us to estimate the direction of the intracellular current flow or, in other words, the site of depolarization in the apical dendrite of large pyramidal neurons in the cerebral cortex. In the report by Mima and colleagues,\textsuperscript{47} in four cases whose EEG showed a positive–negative biphasic activity, the MEG demonstrated a posteriorly directed current flow in the precentral gyrus, suggesting the depolarization in the deep layer of the apical dendrite of the pyramidal neurons in the anterior bank of the central sulcus (area 4). In the remaining two cases, whose EEG showed a monophasic negative activity localized to the contralateral central region, the MEG showed an anteriorly directed current flow in the precentral gyrus, suggesting the depolarization in the superficial layer of the apical dendrite (Fig. 6 of Mima and colleagues\textsuperscript{47}).

Periodic myoclonus seen in CJD seems to be linked only loosely with PSD, if any, because a negative sharp wave demonstrated by back-averaging EEGs time-locked to the myoclonus is much smaller than the PSD which is seen on the raw EEG. As described previously, this is most likely due to significant time jitter between the central and peripheral activities. Moreover, the PSD precedes the onset of myoclonus of an upper extremity by 50 to 85 ms, which is too long for impulse conduction from the primary motor cortex to the peripheral muscle via the corticospinal tract.\textsuperscript{70} In an autopsy-proven case of Gerstmann–Straussler–Scheinker disease which clinically manifested myoclonus but did not show any PSD on the routine EEG, jerk-locked back averaging disclosed a sharp negative potential time-locked to the myoclonus, which seems to correspond to PSD in terms of the waveform and scalp distribution.\textsuperscript{70}

Wilkins and colleagues\textsuperscript{89} reported a group of patients whose myoclonic jerks were generally of small amplitude and multifocal (minipolymyoclonus), preceded by a bilaterally synchronous, frontocentrally predominant, negative slow wave. They proposed the term “primary generalized epileptic myoclonus” for this condition.

Essential myoclonus is not associated with any special EEG activity, even if the jerk-locked averaging technique is applied.\textsuperscript{74} Dystonic myoclonus is usually not accompanied by any EEG correlates with an exception of that seen in SSPE, in which case the quasi-periodic dystonic myoclonus is closely linked with the EEG complexes.\textsuperscript{36} Palatal or oculopalatal myoclonus (palatal tremor) and spinal myoclonus have no special EEG correlates.

**CORTICO-MUSCULAR COHERENCE**

This analysis is also based on the simultaneous recording of EEG and EMG while myoclonic jerks in question are frequently occurring, and is expressed as a correlation of rhythmic activities of certain frequency bands between EEG and EMG. By applying this analysis method to patients with cortical myoclonus, Brown and colleagues\textsuperscript{46} found an abnormally increased coherence for a much higher frequency range. In addition, EEG–EMG coherence for the frequency band of around 20 Hz, which is seen in normal subjects during sustained muscle contraction, was also found. By contrast to the conventional method of jerk-locked back averaging, which requires averaging of a considerable number of sweeps and hence takes a relatively long time (although it depends on the patient’s condition), this analysis method can be applied to a relatively short segment of the EEG–EMG polygraph. However, since the recording is usually performed during sustained muscle contraction, the results of analysis inevitably contain the background activities due to voluntary muscle contraction in addition to the activities directly related to myoclonic jerks. Brown and colleagues\textsuperscript{46} have reported that an abnormal EEG–EMG coherence can be found in some cases where back averaging was unrevealing. They applied this technique to five patients with clinically probable CBD, and found negligible cortico-muscular coherence despite a dramatically exaggerated EMG–EMG coherence up to approximately 60 Hz between finger extensors and first dorsal interosseous muscles on the more affected side.\textsuperscript{26} Based on this finding, they
proposed that myoclonus in this condition might not be due to an exaggerated cortical drive.

**EVOKE RESPONSES**

For recording SEPs, the conventional method can be adopted. Electrical shocks are delivered to the median nerve at the wrist as a square-wave pulse of 0.2–0.5 ms duration at a rate of, for example, 1–2 Hz. The stimulus strength is adjusted to 10%–15% above the motor threshold, but in some patients with cortical reflex myoclonus, the motor threshold is difficult to determine accurately because of significantly lowered threshold of the long-latency reflex, which obscures the direct motor response (M wave).

In most patients with cortical reflex myoclonus, the SEP to electrical stimulation of the peripheral nerve shows a characteristic waveform, its main feature being an extreme enlargement of early cortical components (Fig. 6). Actually, a marked enlargement of SEP in those patients enables its constituent

![Figure 6](image_url)
components to be distinguished more easily than the normal SEP.\(^{35,71}\) The initial component, which consists of a postcentral negative peak N20 and a precentral positive peak P20, is usually not enhanced.\(^{38,59,74,75}\) In MEG recording, however, the magnetic field corresponding to this initial SEP peak (N20m) is also enlarged in some cases, although to a much lesser degree than other components.\(^{41-48}\) The subsequent components are clearly enlarged to a variable degree depending on the patient. The second identifiable peak (P25) shows a single positive field at the contralateral central region, suggesting a current flow which is radially oriented with respect to the head surface (Fig. 6). The third component is a complex consisting of a precentral negative peak (N30) and a postcentral positive peak (P30), suggesting a probable current flow situated in the posterior bank of the central sulcus and tangentially oriented with respect to the head surface. The fourth component is a negative peak (N35) which shows a similar scalp distribution to that of P25. In fact, the amplitude of these components in patients with cortical myoclonus can be more than 10 times as large as the normal value.\(^{38,74,75}\) Scalp topography of each component suggests that the giant SEP may result from an excessive enhancement of physiological components of the normal SEP, instead of occurrence of an abnormal component.\(^{38,71}\)

The study of the somatosensory evoked magnetic fields in patients with cortical or cortical reflex myoclonus discloses abnormalities of the somatosensory areas with relatively high temporal and spatial resolution.\(^{41,48,80,84}\) Among the somatosensory areas, only the primary somatosensory cortex (SI) is hyperexcitable in those cases, whereas the second somatosensory area (SII), located in the upper bank of the sylvian fissure with bilateral innervation, is not.\(^{48}\) Furthermore, within the SI, area 3b, which receives mainly a tactile input, is most sensitive. By applying an instrument devised to activate proprioceptive receptors selectively,\(^{60}\) Mima and colleagues\(^{69}\) showed that area 3a, which receives a proprioceptive input, is also sensitive in those patients. As for nociceptive input, by applying a CO\(_2\) laser beam, which selectively activates the nociceptive receptors, Kakigi and colleagues\(^{89}\) showed that the pain SEP is not enhanced in patients with cortical reflex myoclonus even when they show giant SEP in response to electrical stimulation of peripheral nerves. Until recently, it has been believed that the nociceptive inputs are received mainly in the SII.\(^{51,90,91}\) Recent MEG as well as electrocorticographic studies clearly demonstrate that the SI also receives the nociceptive input.\(^{37,40}\) It is especially noteworthy that, within the SI, its crown (probably the area 1) was shown to be the main receptive field of the nociceptive input.\(^{37,40}\) Thus the current consensus is that areas 3b and 3a, but not area 1, are hyperexcitable in cortical reflex myoclonus.

The ECD of the initial peak of the somatosensory evoked magnetic fields (N20m) is localized in the posterior bank of the central sulcus, most likely in area 3b. As for the next SEP component (P25) or its MEG counterpart (P25m), which is clearly enlarged in the patients with cortical or cortical reflex myoclonus (Fig. 7), its dipole source is usually identified in the precentral gyrus.\(^{48}\) In this case, the intracellular current flow in the apical dendrite of the pyramidal neurons is estimated to be directed posterolaterally, suggesting that it represents the depolarization in the deep layer of the apical dendrite situated either in the anterior bank of the central sulcus (area 4) or in the crown of the precentral gyrus. As for the mechanism of detection by MEG of a radially oriented dipole in the crown (which theoretically cannot be recorded as magnetic fields from the head surface), it is conceivable that the tangential vector of the radially oriented dipole is picked up as an MEG signal as a result of its extreme enlargement.\(^{48}\) This contrasts with the generator mechanism of N20 or N20m which shows anteromedially directed intracellular current flow in the postcentral gyrus (area 3b), indicating depolarization occurring in the deep layer of the tangentially oriented apical dendrite of the somatosensory neurons in that area.

Since the giant SEP is not seen in other types of myoclonus, its demonstration is clinically significant for supporting the clinical diagnosis of cortical or cortical reflex myoclonus. However, short-latency SEP components, which occur within 20 ms after median nerve stimulation at the wrist and are known to be generated in subcortical structures, are not enhanced in any type of myoclonus.

Patients with photosensitive myoclonus show giant evoked potentials at occipital as well as fronto-central electrodes in response to flash stimulation.\(^{72}\) Questions as to where in the frontal lobe this anterior response is generated, and whether the anterior response is mediated by the primary occipital response or the result of direct input from the thalamus to the frontal cortex remain to be elucidated.

Besides the analysis of evoked electrical or magnetic fields following peripheral stimulation, the change of cortical rhythmic oscillations following stimulation can also be analyzed. Silen and colleagues\(^{76}\) studied rhythmic oscillations over the hand area of the sensorimotor cortex following electrical stimulation of the median nerve. In normal subjects,
they found a small transient decrease followed by a rebound increase of 20 Hz oscillations, but this rebound increase was absent in patients with Unverricht–Lundborg type PME. They ascribed the lack of 20 Hz rebound to decreased cortical inhibition. Recently, high-frequency oscillations (HFOs) of several hundred hertz and their abnormality in various movement disorders have drawn increasing attention. Mochizuki and colleagues studied the somatosensory evoked HFOs in four patients with myoclonus epilepsy, and found enhancement of late HFOs of 600–750 Hz frequency range.

**LONG-LOOP REFLEX**

The long-latency, long-loop reflex can be recorded using the same EMG electrode placement as used for jerk-locked back averaging. Modality of the stimulus is selected based on clinical observation, but electrical shocks delivered to the median nerve at the wrist are most commonly used. In this case, the EMG response is best recorded from the thenar muscle of the stimulated hand, but can be recorded also from other muscles of the stimulated upper extremity or even from those of the nonstimulated extremities with different latencies. When studying the long-loop reflex, it is extremely important and effective to record cortical evoked potentials simultaneously.

In cortical reflex myoclonus, a markedly enhanced long-latency reflex is usually recorded from the thenar muscle at a latency of around 45 ms after stimulation of the median nerve at the wrist. This enhanced long-loop reflex corresponds to the C reflex named by Sutton and Mayer. Most patients show both giant SEPs and C reflex. In most cases of cortical reflex myoclonus, the larger the SEP, the more conspicuous and widespread is the C reflex. In some cases, however, these two phenomena do not necessarily correlate with each other in terms of magnitude.

In some patients, the enhanced C reflexes can be recorded also from more proximal muscles of the stimulated upper extremity with shorter latency and even from the opposite (nonstimulated) hand muscle. In the latter case, the latency difference of C reflexes was 50–80 ms.

**FIGURE 7.** Somatosensory evoked magnetic fields (MEG, magnetoencephalogram) and potentials (EEG, electroencephalogram) following electrical stimulation of the right median nerve at wrist in a patient with familial cortical myoclonic tremor. Lt, left. (By courtesy of Dr. Tatsuya Mima.)
reflexes between the left and right hand muscles is 10 to 15 ms. This time lag seems to be compatible with the conduction time of the impulse between the homologous cortical areas of two hemispheres through the corpus callosum.

The time interval from the P25 peak of the giant SEP to the onset of the enhanced C reflex is similar to or slightly longer than the interval from the initial positive peak of the myoclonus-related cortical spike to the onset of the spontaneous myoclonus. Based on the similarity in time intervals as well as the scalp topography, the giant SEP and myoclonus-related cortical spike are postulated to share at least some common physiological mechanisms.

Long-latency, long-loop reflexes can be recorded following the stimulus presentation of other modalities such as flash. Photic reflex myoclonus seems to be mediated by the cerebral cortex. Because the onset latency of the occipital and frontal responses is around 35 and 40 ms, respectively, and because the occipital response is also enlarged, it is most likely that the reflex arc involves the occipitofrontal pathway.

Shibasaki and colleagues reported that in some patients with cortical reflex myoclonus, electrical stimulation of the median nerve at the extended wrist elicited abrupt wrist drop associated with a short interruption of the EMG discharges. Furthermore, it was found that the larger the SEP, the longer was the elicited EMG silent period, thus causing more conspicuous wrist drop. Moreover, the silent period was also induced in the EMG of the opposite (nonstimulated) hand, particularly when the giant SEP was also recognized over the central region ipsilateral to the stimulus. Thus, it was suggested that this phenomenon might be a negative myoclonus induced via the transcortical reflex pathway, and it was called "cortical reflex negative myoclonus" as a negative counterpart of the more conventional form of cortical reflex myoclonus, cortical reflex positive myoclonus. Negative myoclonus can be induced by stimulation of other modalities as well. Gambardella and colleagues reported a case of photically induced epileptic negative myoclonus.

In reticular reflex myoclonus, the long-latency reflex is enhanced, but cortical evoked potentials are not enhanced. In this condition, the reflex myoclonus first involves bulbar muscles such as the sternocleidomastoid and trapezius muscles, and subsequently the more rostral cranial muscles (such as the facial muscles) and caudal muscles (such as limb muscles) are involved. A great variability of the reflex latency among myoclonic jerks within an individual subject seems to be characteristic of this form of reflex myoclonus, indicating the necessity for looking at individual responses to a single stimulus rather than averaging.

Spinal myoclonus, whether segmental or propriospinal, can be stimulus sensitive. In spinal myoclonus, therefore, it is worthwhile presenting various mechanical stimuli, such as tapping the muscle or tendon, while recording EMGs from multiple muscles.

**PAIRED STIMULATION EVOKED POTENTIALS AND LONG-LOOP REFLEX**

By employing a paired median nerve stimulation SEP technique with various ISIs in a patient with cortical reflex myoclonus, Dawson found a depression of cortical excitability at a latency between 10 and 30 ms, enhancement between 60 and 100 ms, and then another depression. Sutton and Mayer found a mild enhancement of cortical excitability between 32 and 63 ms and also between 130 and at least 250 ms in a patient with focal cortical reflex myoclonus. Simultaneous recording of long-latency reflexes in a paired stimulation paradigm provides further information regarding the mechanism of...
the reflex myoclonus. Demonstration of a short period of enhanced cortical excitability following a single stimulus supports the participation of the cerebral cortex in generation of that particular reflex myoclonus, and furthermore, it may explain the occurrence of two successive giant positive peaks of SEPs and two successive C reflexes following a single stimulus in some patients.

For recording the paired stimulation SEPs and long-latency reflex, the same set-up used for recording the SEP and long-latency EMG reflex can be used. Any ISI can be chosen; for example, an initial interval of 5 ms followed by a stepwise increase by 10 ms up to 50 ms and then by 25 to 50 ms up to 200 ms. Paired stimulation in other modalities, such as flash, can also be employed.

Subtraction of the response to a single stimulus from that to paired stimuli is usually necessary for obtaining a recovery function of cortical excitability, but when dealing with a giant evoked potential, subtraction may not be needed except at very short ISIs.

**JERK-LOCKED EVOKED POTENTIALS**

This technique can be used to study whether there is any change in cortical excitability following a spontaneous myoclonic jerk. The stimulus is presented just at the time of, or at varying intervals after, the onset of the EMG discharge associated with spontaneous myoclonus. EEGs and the rectified EMG are then averaged by using the EMG onset as a trigger. A cortical excitability curve after myoclonus can be obtained by comparing the amplitude of a certain component of the evoked potentials thus recorded with that of control evoked potentials obtained by presenting the same stimulus with a random time relationship to the myoclonus.

By using this technique in a patient with PME, Shibasaki and colleagues reported a similar enhancement of cortical excitability of 20-ms duration immediately after the myoclonus-related cortical spike, as well as after the giant SEP; the latter is being studied by the paired stimulation SEP technique. This finding supports the hypothesis that the myoc-
lonus-related cortical activity in cortical reflex myoclonus is generated by a mechanism common to that of the giant SEP. In a patient with CJD, cortical excitability was suppressed between periodic myoclonic jerks or between consecutive PSDs, suggesting that the periodicity might be related, at least partially, to a refractoriness of the cerebral cortex. In a patient with oculopalatal-somatic myoclonus (tremor) due to a pontine lesion, there was no change of cortical excitability in relation to the rhythmic movements, suggesting that this type of involuntary movement is not related to the excitability change of the cerebral cortex.

TRANSCRANIAL MAGNETIC STIMULATION

For the last 15 years, the technique of TMS has been applied extensively to the investigation of pathophysiology of various movement disorders. Since the excitability change of the sensorimotor cortex is involved in many cases of cortical or cortical reflex myoclonus as its physiological background, TMS is especially useful for directly investigating the excitability change of the motor cortex. Reutens and colleagues applied TMS preceded by electrical stimulation of the median nerve at various intervals to patients with PME and found increased excitability at approximately 50 ms after the peripheral nerve stimulation. Later, Cantello and colleagues used the same technique and found MEP facilitation at ISIs of 34–60 ms. In order to elucidate the modality specificity of the peripheral stimulation, Manganotti and colleagues used electrical stimulation of digital nerve delivered at three times the sensory threshold followed by TMS in patients with PME. They found facilitation at ISI of 25–40 ms, whereas a significant MEP inhibition was seen from 25–50 ms in normal subjects (Fig. 10). In contrast, Valzania and colleagues

![Figure 10](image1.png)

**FIGURE 10.** Motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) following electrical stimulation of the digital nerve by various interstimulus intervals (ISIs) in a healthy control subject (left) and in a patient with progressive myoclonus epilepsy (PME) (right). Note the enhancement of MEP by the conditioning stimulus given 20–50 ms before the TMS in the patient versus its suppression in the normal subject. (From Manganotti and colleagues with permission.)

![Figure 11](image2.png)

**FIGURE 11.** Motor evoked potentials (MEPs) elicited by paired pulse transcranial magnetic stimulation (TMS) at interstimulus interval (ISI) of 50 ms in a normal subject (upper trace) and in a patient with progressive myoclonus epilepsy (PME) (lower trace). Note a remarkable enhancement of excitability at 50 ms after the conditioning stimulus in the patient. (From Valzania and colleagues with permission.)
leagues applied paired-pulse TMS at 110% of the resting motor threshold for both stimuli to patients with PME, and found facilitation at 50 ms, in contrast with normal subjects (Fig. 11). Brodtmann and colleagues applied paired-pulse TMS to patients with generalized epilepsy and found markedly enhanced excitability in a patient with juvenile myoclonic epilepsy when the second stimulus was given 250 ms after the first. Hanajima and colleagues studied the supra-threshold conditioning TMS delivered to the primary motor cortex’s effect on the excitability of the opposite hemisphere’s primary motor cortex in five patients with benign myoclonus epilepsy. They found an absence of the transcallosal late inhibition which is seen at ISI of 8–20 ms in normal subjects, suggesting an abnormal cortical inhibitory mechanism in cortical myoclonus. Thus, TMS clearly shows abnormal excitability of the motor cortex in cortical myoclonus.

CONCLUSION

Just like other involuntary movements, the study of myoclonus should start with careful clinical observation with special attention directed to the site of involvement, rhythmicity or periodicity, provoking factors, stimulus sensitivity, mode of effective stimuli if stimulus sensitive, and accompanying neurological signs. Electrophysiological studies as described above are useful to delineate further characteristics of the myoclonus. The EEG–EMG polygraph is the most useful technique because it provides the most important information about the myoclonus in each patient. Jerk-locked back averaging and evoked potential studies combined with recording of the long-latency, long-loop reflexes are then useful to clarify the pathophysiology of myoclonus, especially that of cortical myoclonus. Furthermore, these techniques can be combined to investigate the precise role of the cerebral cortex in the generation of myoclonus. Recent advances in MEG techniques have contributed significantly to the elucidation of some of the cortical mechanisms underlying myoclonus. Recent advances in the application of TMS have greatly contributed to the understanding of the motor cortex excitability change in cortical myoclonus. Elucidation of physiological mechanisms underlying myoclonus in each individual patient is important for selecting the most appropriate treatment of choice.

REFERENCES

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