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UPDATE

Unravelling the enigma of cortical tremor and other forms of cortical myoclonus

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Cortical tremor is a fine rhythmic oscillation involving distal upper limbs, linked to increased sensorimotor cortex excitability, as seen in cortical myoclonus. Cortical tremor is the hallmark feature of autosomal dominant familial cortical myoclonic tremor and epilepsy (FCMTE), a syndrome not yet officially recognized and characterized by clinical and genetic heterogeneity. Non-coding repeat expansions in different genes have been recently recognized to play an essential role in its pathogenesis. Cortical tremor is considered a rhythmic variant of cortical myoclonus and is part of the 'spectrum of cortical myoclonus', i.e. a wide range of clinical motor phenomena, from reflex myoclonus to myoclonic epilepsy, caused by abnormal sensorimotor cortical discharges. The aim of this update is to provide a detailed analysis of the mechanisms defining cortical tremor, as seen in FCMTE. After reviewing the clinical and genetic features of FCMTE, we discuss the possible mechanisms generating the distinct elements of the cortical myoclonus spectrum, and how cortical tremor fits into it. We propose that the spectrum is due to the evolution from a spatially limited focus of excitability to recruitment of more complex mechanisms capable of sustaining repetitive activity, overcoming inhibitory mechanisms that restrict excitatory bursts, and engaging wide areas of cortex. Finally, we provide evidence for a possible common denominator of the elements of the spectrum, i.e. the cerebellum, and discuss its role in FCMTE, according to recent genetic findings.

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Abbreviations: EPC = epilepsia partial continua; FCMTE = autosomal dominant familial cortical myoclonic tremor and epilepsy

Introduction

In 1990, Ikeda and colleagues described two patients with 'shivering-like tremor in fingers and/or hands in the outstretched posture and aggravated by action' (Ikeda *et al.*, 1990). Although patients were clinically diagnosed as 'essential tremor', beta-blocker unresponsiveness and other atypical features made the authors question their diagnosis.

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Further electrophysiological tests disclosed action tremor, linked to increased sensorimotor cortex excitability, as found in cortical myoclonus. They called this 'cortical tremor', which is in fact a rhythmic variant of cortical myoclonus. Thereafter, similar cases were reported in over 100 pedigrees worldwide, enabling the characterization of a cortical tremor syndrome, currently known as autosomal dominant familial cortical myoclonic tremor and epilepsy (FCMTE), with well-known clinical features but still uncertain pathophysiology and genetic aetiology. Interestingly, recent genetic discoveries have shown that non-coding repeat expansions in different genes play an essential role in its pathogenesis; however, the reason for the clinical and genetic heterogeneity that characterizes the syndrome is still unclear.

The aim of this update is to clarify the pathophysiology of cortical tremor defined as a rhythmic oscillation involving the upper limbs, bilaterally and distally, during posture or action, that fulfils the electrophysiological criteria of cortical myoclonus (Latorre *et al.*, 2018); i.e. the cardinal clinical feature of FCMTE. A detailed description of the mechanisms underlying cortical tremor are given on the basis of pathophysiological evidence and recent genetic findings. After a brief review of clinical and genetic features of FCMTE, we discuss how cortical tremor fits into the 'spectrum of cortical myoclonus' (Obeso *et al.*, 1985); namely a pathophysiologically-related continuum of motor phenomena, from cortical myoclonus to myoclonic epilepsy, including cortical tremor, resulting from abnormal discharges in the sensorimotor cortex. We therefore speculate on the possible mechanisms that generate the discrete clinical elements within this spectrum and provide evidence for a common denominator, i.e. the cerebellum. We end by discussing the role of the cerebellum in FCMTE, according to the new genetic data.

Autosomal dominant familial cortical myoclonic tremor and epilepsy

Although it is not yet officially recognized by the International League Against Epilepsy and its nosological placement is still debated, FCMTE is a well-delineated condition characterized by the association of cortical tremor, cortical myoclonus and epileptic seizures, inherited in an autosomal dominant pattern and with genetic heterogeneity (Striano *et al.*, 2005; van den Ende *et al.*, 2018).

Cortical tremor

Cortical tremor, also known as rhythmic cortical myoclonus, is a small amplitude, rhythmic oscillation involving the distal upper limbs during posture and action, and rarely present at rest (Okuma *et al.*, 1998; Guerrini *et al.*, 2001; van Rootselaar *et al.*, 2002). The jerks can also involve legs, head, trunk, proximal upper limbs and facial muscles, especially the eyelid· (Inazuki *et al.*, 1990; Guerrini *et al.*, 2001; van Rootselaar *et al.*, 2002). Cortical tremor can be stimulus-sensitive to touch and photic stimulation (van Rootselaar *et al.*, 2005; Suppa *et al.*, 2009; Crompton *et al.*, 2012). Onset is typically in the second or third decade (range: 3–70 years) (van den Ende *et al.*, 2018).

The electrophysiological distinction between tremor and myoclonus is based on the rhythmicity of the jerks. In tremor, motor unit activity is synchronized at a specific frequency (i.e. rhythmic) and strong enough to produce a clear peak in the EMG power spectrum. EMG recording of myoclonus, in contrast, shows arrhythmic bursts of variable duration, depending on the source. In patients with FCMTE, both rhythmic tremulous and arrhythmic myoclonic jerks can be recorded, the latter having a larger range of frequencies (Guerrini *et al.*, 2001; Striano *et al.*, 2005; van den Ende *et al.*, 2018). EMG discharges are synchronous between agonist and antagonist muscles, being of ~50-ms duration (Ikeda *et al.*, 1990; Guerrini *et al.*, 2001; Striano *et al.*, 2005). Unlike other forms of tremor, the rhythmic jerks recorded in FCMTE fulfil the electrophysiological criteria of cortical myoclonus (Latorre *et al.*, 2018), namely EEG discharges time-locked to individual myoclonic jerks, giant cortical somatosensory evoked potentials (SEP) and enhanced long-latency reflexes (Fig. 1). These findings suggest that the movements are generated by an abnormal sensorimotor discharge and that cortical tremor is a rhythmic form of cortical myoclonus.

Cortical tremor has rarely been described in diseases other than FCMTE (Guerrini *et al.*, 1996; Schulze-Bonhage and Ferbert, 1998; Botzel and Werhahn, 1999; Wang *et al.*, 1999) and in patients with no other neurological abnormalities (Toro *et al.*, 1993); however, in some of these cases, it is difficult to distinguish it from epilepsia partial continua (EPC). Asterixis (known as flapping tremor) is a form of myoclonus that might be confused with cortical tremor. However, unlike cortical tremor, asterixis is represented by sudden, brief, arrhythmic lapses of sustained posture due to involuntary interruption in muscle contraction (negative myoclonus) (Ellul *et al.*, 2017).

Other clinical features of autosomal dominant familial cortical myoclonic tremor and epilepsy

Epilepsy commonly associates with cortical tremor, although it is not always present and not necessary for the diagnosis of FCMTE. Seizures occur in the third or fourth decade, usually post-dating cortical tremor. Seizures are typically generalized tonic-clonic (GTCS), but myoclonic seizures are also described (van Rootselaar *et al.*, 2002; Licchetta *et al.*, 2013). Seizure frequency is usually low, but severe cases and drug-resistant epilepsy are recognized (Guerrini *et al.*, 2001; Carr *et al.*, 2007).

Cognitive impairment is frequent in FCMTE families (Guerrini *et al.*, 2001; Suppa *et al.*, 2009; Sharma *et al.*, 2014; Zeng *et al.*, 2015). While ataxia is not classic in FCMTE, other cerebellar signs (gait instability, downbeat

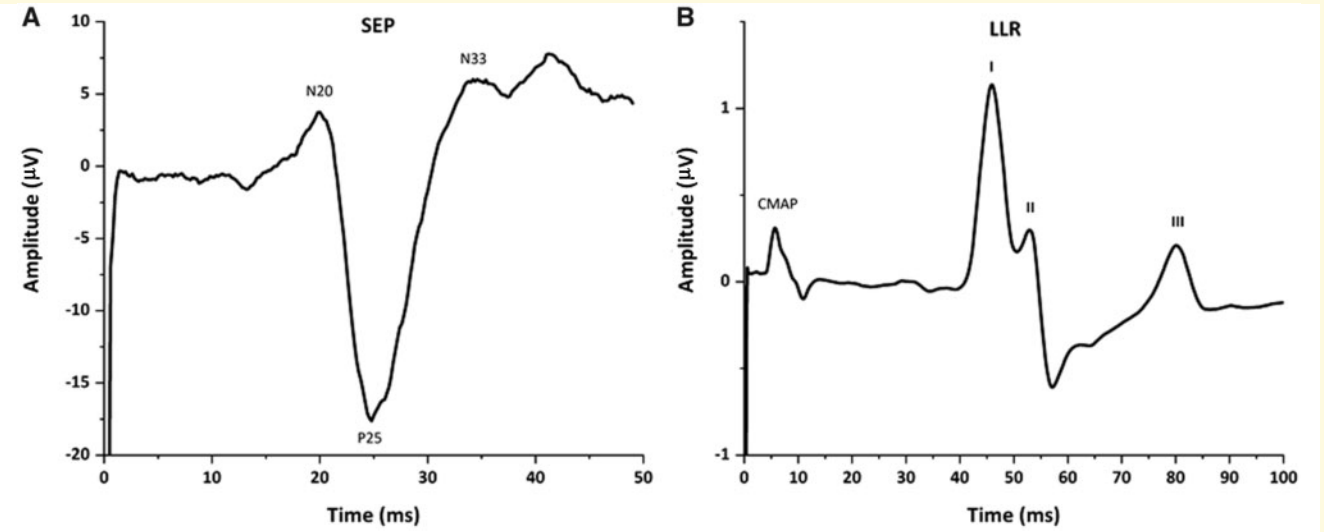

Figure 1 Somatosensory evoked potentials and a long-latency reflex example. (**A**) Somatosensory evoked potentials (SEP) showing a giant N20-P25 and P25-N33 components (single patient recording). (**B**) Long-latency reflex (LLR) traces showing a large EMG activity compatible with a C-reflex with onset around 40 ms, and LLR II and LLR III with onset around 50 ms and 75 ms, respectively. CMAP = compound muscle action potential.

nystagmus, dysarthria) do feature (van Rootselaar *et al.*, 2005; Magnin *et al.*, 2009; Sharma *et al.*, 2014; Gao *et al.*, 2016). Other clinical findings include migraine (Saka and Saygi, 2000; Crompton *et al.*, 2012), night blindness (possibly due to an alteration in calcium-mediated neurotransmitter release from photoreceptors in response to light) (Manabe *et al.*, 2002), motionless state (Morita *et al.*, 2003) and parkinsonism (Terada *et al.*, 1997; Marti-Masso *et al.*, 2013). Psychiatric co-morbidity, particularly mood, anxiety disorders and schizophrenia, are noted in some families (Deng *et al.*, 2005; Coppola *et al.*, 2011; Licchetta *et al.*, 2013; Mahadevan *et al.*, 2016).

Genetics

FCMTE shows locus heterogeneity although recent findings suggest a common molecular pathology. The first locus (FCMTE1) mapped to chromosome 8q23.3-q24.11 in a three-generation Japanese pedigree with classic clinical and electrophysiological findings (Mikami *et al.*, 1999). At least 60 Japanese and 23 Chinese kindreds with FCMTE related to 8q24 chromosome region have been reported, and variants in *SLC30A8* (8q24.11) [but its pathogenicity was then not supported *in silico* study (Cen *et al.*, 2015)], *DCAF13* (8q23.3) and *NOV* (8q24.12), all co-segregating with FCMTE in Chinese kindreds, have been found (Cen *et al.*, 2018; Ishiura *et al.*, 2018; Lin *et al.*, 2018; Lei *et al.*, 2019).

The second locus (FCMTE2), principally identified in Italian (but also Spanish and Austrian) families, mapped to chromosome 2p11.1-q12.2 (Guerrini *et al.*, 2001; De Falco *et al.*, 2003; Striano *et al.*, 2004, 2005; Madia *et al.*, 2008; Saint-Martin *et al.*, 2008; Suppa *et al.*, 2009; Crompton *et al.*, 2012; Licchetta *et al.*, 2013; Henden *et al.*, 2016). The phenotype is more severe, with some cases exhibiting intractable complex focal seizure and mild-to-moderate intellectual disability. A founder effect likely explains Italian FCMTE2 families from the same geographical area (Madia *et al.*, 2008; Licchetta *et al.*, 2013) and is confirmed in a larger cohort of pedigrees of European ancestry (Henden *et al.*, 2016).

The FCMTE3 locus, linked to chromosome 5p15.31-p15, was described in one French, two Chinese and one Dutch family (Depienne *et al.*, 2010; Li *et al.*, 2014; Liu *et al.*, 2015; van Rootselaar *et al.*, 2017). Patients additionally displayed simple visual hallucinations, transient loss of consciousness without automatisms, and worsening of symptoms due to hypoglycaemia and fatigue (Depienne *et al.*, 2010). Whole exome sequencing (WES) identified a missense variant in the catenin delta 2 gene (*CTNND2*) in the Dutch FCMTE3 pedigree, with functional tests supporting its pathogenicity.

The FCMTE4 locus, mapped to chromosome 3q26.32-3q28, was identified in 2013 by genome-wide linkage study (Yeetong *et al.*, 2013). In 2019, TTTCA and TTTTA pentanucleotide repeat insertions in intron 1 of *YEATS2* (3q27.3) were reported as the causative mutation of FCMTE4 in the original family (Yeetong *et al.*, 2019).

The fifth locus (FCMTE5) was identified in a consanguineous Egyptian kindred exhibiting adolescent-onset recessively inherited cortical tremor, complex focal seizures and/or GTCS (Stogmann *et al.*, 2013). In this pedigree, a single base-pair deletion was detected in *CNTN2* (1q32.1) (Stogmann *et al.*, 2013). However, the classification of this disorder as FCMTE remains controversial (Striano *et al.*, 2013).

Table 1 Genetic and molecular characterization of FCMTE and populations studied

Form	OMIM®#	Inheritance	Chromosome	Candidate gene(s)	Gene product	Population
FCMTE1	601068	AD	8q24.11-q24.12	*SAMD12*	Sterile alpha-motif domain-containing 12	Dozens of Japanese and Chinese pedigrees
FCMTE2	607876	AD	2q11.2-q12.2	*STARD7* [*ADRA2B*]	StAR-related lipid transfer protein 7 Alpha 2-adrenergic receptor subtype b	Twelve Italian, one Spanish, two French, and one New Zealander/Australian (Austrian ancestry) pedigrees
FCMTE3	613608	AD	5p15.31-p15.1	*MARCH6* [*CTNND2*]	E3 ubiquitin-protein ligase Catenin delta 2	One French, one Dutch, and two Chinese pedigrees
FCMTE4	615127	AD	3q26.32-q28	*YEATS2*	YEATS domain containing 2	One Thai pedigree
FCMTE5	615400	AR	1q32.1	*CNTN2*	Contactin 2	One Egyptian pedigree (consanguinity)
FCMTE6	618074	AD	16p12.1	*TNRC6A*	Trinucleotide repeat containing 6A	One Japanese pedigree
FCMTE7	618075	AD	4q32.1	*RAPGEF2*	Rap guanine nucleotide exchange factor 2	One Japanese and one Chinese pedigrees

AD = autosomal dominant; AR = autosomal recessive; OMIM® = Online Mendelian Inheritance in Man.
Candidate genes with weak evidence are reported in brackets.

Anticipation of cortical tremor and/or GTCS has been observed in some FCMTE families, suggesting a repeat expansion disorder (Ikeda *et al.*, 2005; Hitomi *et al.*, 2012, 2013). Interestingly, TTTCA, TTTTA and TTTGA pentanucleotide repeats in intron 4 of *SAMD12* (8q24) have been described as FCMTE1 pathogenic variants in numerous Japanese and Chinese pedigrees (Cen *et al.*, 2018, 2019; Ishiura *et al.*, 2018; Lei *et al.*, 2019; Zeng *et al.*, 2019). The length of expanded repeats showed intergenerational instability and negative correlation with age at onset of both cortical tremor and epilepsy (Ishiura *et al.*, 2018; Zeng *et al.*, 2019).

Pentameric intronic expansions have also been identified at other loci, including ATTTC expansions of *STARD7* (2q11.2-FCMTE2 locus) (Corbett *et al.*, 2019), TTTTA/TTTCA repeat expansions in *MARCH6* (5p15.2-FCMTE3 locus), and in *YEATS2* (FCMTE4) (see above) (Florian *et al.*, 2019; Yeetong *et al.*, 2019).

WES has identified a number of other possible FCMTE-related genes, though none has sufficient evidence of causality (Kato *et al.*, 2012; Marti-Masso *et al.*, 2013; Gao *et al.*, 2016). Interestingly, some of the negative Japanese families tested for expansions in *SAMD12* showed identical TTTCA/TTTTA repeat expansions in *TNRC6A* (FCMTE6) and *RAPGEF2* (FCMTE7), the latter finding having been replicated in one Chinese pedigree (Ishiura *et al.*, 2018; Zeng *et al.*, 2019). Table 1 summarizes genetic and molecular characterization of FCMTEs.

Spectrum of cortical myoclonus

Myoclonus is a brief, jerky involuntary movement arising in the CNS (Obeso *et al.*, 1985) that is produced either by abrupt muscle contraction or sudden cessation of ongoing muscular activity (Marsden *et al.*, 1982). Cortical myoclonus is caused by abnormal electrical discharges arising in the cerebral cortex, as demonstrated by electrophysiology (Latorre *et al.*, 2018). Its manifestations are several and represent a continuum from (i) cortical reflex myoclonus (jerks provoked by sensory input); (ii) spontaneous cortical myoclonus and cortical tremor (arrhythmic and rhythmic jerks respectively, arising spontaneously but often confined to a small group of muscles); and (iii) EPC and myoclonic epilepsy, characterized by more widespread abnormal cortical activity (Obeso *et al.*, 1985).

All of these clinical syndromes share a common electrophysiological hallmark, i.e. a sudden and brief activation of the corticospinal tract (CST) neurons. Negative myoclonus may result from a sudden interruption of activity in CST neurons, although spinal inhibitory mechanisms may contribute (Inghilleri *et al.*, 1993). Although CST neurons are a common element in all forms of cortical myoclonus, it is not known whether they are ever the source of the abnormal activity, or whether they are passive elements that respond to abnormal input generated elsewhere. Additionally, as the bursts of activity are so brief, there must also be a powerful inhibitory mechanism that terminates the excitation.

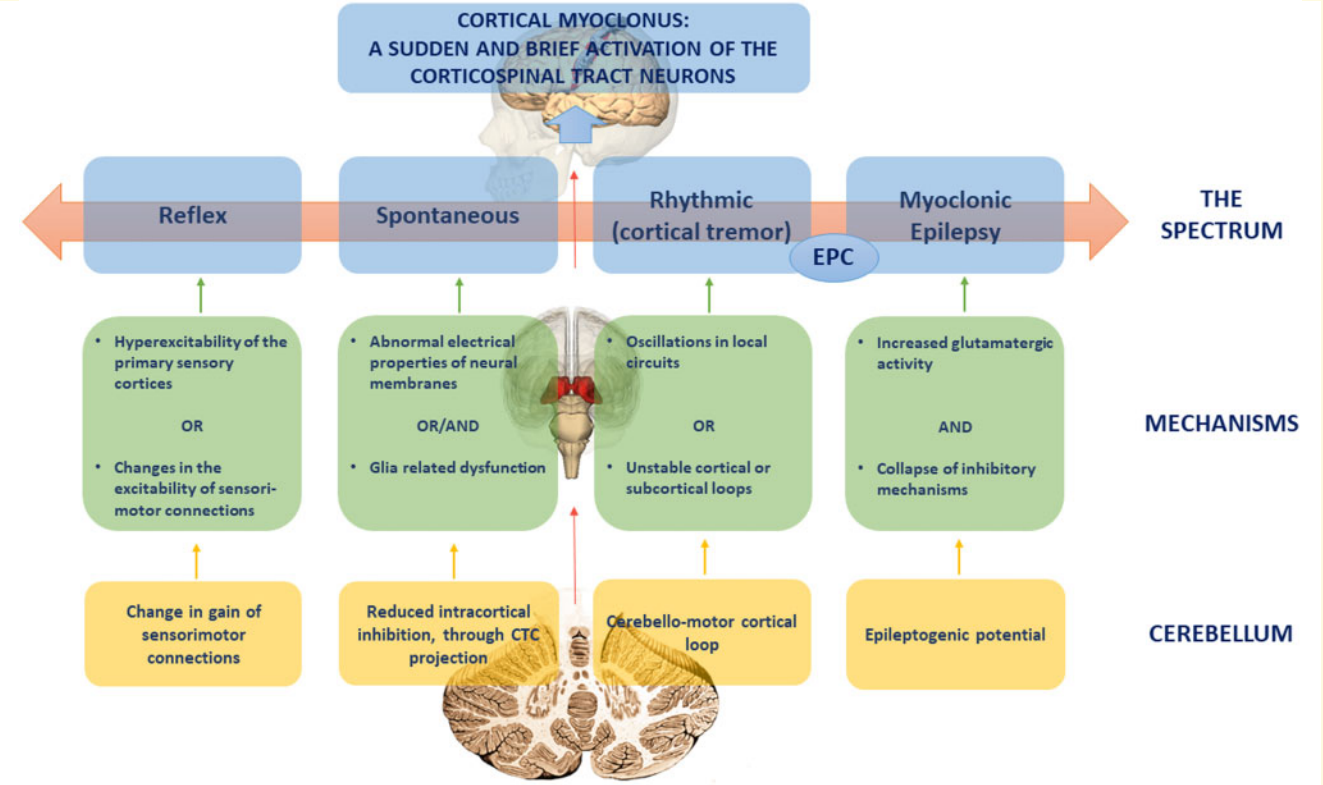

Figure 2 Summary of the pathophysiological mechanisms causing cortical myoclonus. The red arrows, linking the images in the background, represent the cerebello-thamalo-cortical (CTC) projection.

We propose that the spectrum of cortical myoclonus, from localized reflex jerks to widespread activation of the whole sensorimotor cortex and beyond, is due to the evolution from a spatially limited focus of heightened excitability to recruitment of more complex mechanisms that are capable of sustaining repetitive activity, overcoming inhibitory mechanisms that restrict excitatory bursts, and engaging wide areas of cortex. Figure 2 gives a simple summary of the mechanisms described.

In the case of cortical reflex myoclonus, a normal volley of afferent input is transformed at some point in a sensorimotor loop into an abnormal burst of excitation. Evidence from somatosensory- and visually-triggered jerks suggests that this could occur either within the primary somatosensory (S1) or visual cortex (V1) or in their connections with the motor cortex. For example, in photic reflex myoclonus, there are abnormalities in contrast gain (Porciatti *et al.*, 2000) and clustering of gamma-band oscillations (Parra *et al.*, 2003). Similarly, in the somatosensory cortex, giant SEP usually confirm S1 hyperexcitability (Shibasaki and Hallett, 2005). Changes in the excitability of sensorimotor connections have also been described (Strigaro *et al.*, 2015). Visually-evoked muscle jerks are associated with transients in contralateral central regions time-locked with flash stimuli (Rubboli *et al.*, 1999), in the absence of any evidence of hyperexcitability in V1 (Shibasaki and Neshige, 1987). Although the mechanisms behind this abnormal connectivity are unknown, abnormal LTP-like plasticity in motor cortical areas induced by visual stimulation is possible (Suppa *et al.*, 2015*a*, *b*). Similar evidence in somatosensory reflex myoclonus is lacking; however, the presence of enhanced long-latency reflexes, commonly associated with giant SEP, can be considered as a marker of abnormal interaction between S1 and primary motor cortex (M1) (Fig. 2).

The pathophysiology of spontaneous myoclonus, cortical tremor and EPC is clearly different. The spontaneous jerks observed in these conditions imply an intrinsic tendency to bursts of either excitatory or inhibitory activity (producing positive or negative jerks). One possibility is that the resting membrane potential of some population(s) of excitatory or inhibitory neurons lies closer to threshold than normal, the latter being reached intermittently due to random fluctuations in input. Alternatively, it might be due to abnormal electrical properties of neural membranes caused by changes in ion channel properties or in postsynaptic receptors, as in several epilepsy phenotypes (Villa and Combi, 2016; Perucca and Perucca, 2019). It is also tempting to speculate that functional alterations of glia might be at play. For instance, it has been demonstrated that increasing extracellular potassium is sufficient to induce epileptiform activity in

hippocampal slices from animals or humans (Traynelis and Dingledine, 1988; Gabriel *et al.*, 2004). Failure of glia to adequately buffer electrolytes and excitatory neurotransmitters might therefore lead to neuronal hyperexcitability and generation of spontaneous jerks (Patel *et al.*, 2019) (Fig. 2).

Such mechanisms should produce jerks that occur relatively randomly. However, the more rhythmic jerking of cortical tremor (and often EPC), requires additional explanation. Two possibilities should be entertained. First, there could be oscillations in local circuits linking CST neurons and interneurons. In this regard, it is worth noticing that feedback inhibition might be more suited to sculpt network activity and generate clusters of activation that appear as patterns in local field potential (Lytton and Omurtag, 2007). Alternatively, rhythmicity may not come from local interactions but may result from oscillations in more distant connections, such as unstable cortical loops (particularly in EPC, where there can be extensive cortical damage) (Mameniskiene and Wolf, 2017) or subcortical structures, such as in parkinsonian and essential tremor (Hallett, 2014). It is known that at least two regions within the central motor pathways, i.e. the inferior olive and the relay nuclei of the thalamus, can demonstrate oscillatory behaviour, due to a combination of intrinsic properties of ion channels in individual neurons and because of the way the latter neurons are interconnected within CNS circuits (Rothwell, 1998). Thus, jerk rhythmicity in cortical tremor and EPC could be explained by an interaction between local factors within M1 and synchronization by external sources (Fig. 2).

As noted above, in most cases the cortical discharges remain localized. However, there are examples in which both reflex and spontaneous jerks appear to spread within the motor cortex of one hemisphere, as well as between the two hemispheres, generating multifocal or generalized jerking. Indeed, in myoclonic epilepsy, abnormal discharges sometimes give rise to generalized seizures. It is reasonable to assume that, during the recruitment of new territories to a starting cortical discharge, the driving force is provided by glutamatergic output (Parrish *et al.*, 2019) and is usually terminated both temporally and spatially by a powerful inhibition (Schevon *et al.*, 2019). Our interpretation is that in the case of generalized jerks and myoclonic epilepsies, the spatial progression of ictal activity coincides with a collapse of inhibition (Trevelyan *et al.*, 2006, 2007; Ahmed *et al.*, 2014). The mechanisms of this inhibitory collapse might include perturbations in chloride homeostasis (Huberfeld *et al.*, 2007; Pallud *et al.*, 2014) and interneuronal depolarization block due to excessively strong excitatory input (Bikson *et al.*, 2003). However, the conditions that precipitate this effect, and its precise role in spreading ictal activity, remain unclear (Fig. 2).

The role of the cerebellum

In the context of cortical myoclonus, the cerebellum deserves special mention. Cerebellar ataxia is a prominent feature in several conditions associated with cortical myoclonus (Ganos *et al.*, 2014) and pathological findings in cortical myoclonus often involve the cerebellum (Bhatia *et al.*, 1995; Tijssen *et al.*, 2000). We speculate that the cerebellum could contribute to cortical myoclonus in a variety of ways (Fig. 2).

Recent experiments have shown that the gain of long latency stretch reflexes (LLSR) is adjusted to changes in task demands when movements adapt to different external conditions (Pruszynski and Scott, 2012; Omrani *et al.*, 2014). Given the prominent role of the cerebellum in motor adaptation, it seems likely that cerebellar inputs play an important part in this gain control. If so, this could explain why abnormalities of cerebellar function are frequently associated with heightened LLSRs and reflex myoclonus (Diener *et al.*, 1984; Rodriguez *et al.*, 1994; Shibasaki and Thompson, 2011). We propose that abnormal activity in the cerebello-thalamo-cortical projection could change the gain of sensorimotor connections and cause reflex myoclonus (Ganos *et al.*, 2014). The mechanism could, for example, involve the known cerebello-cortical projections to local inhibitory systems, which have been indirectly demonstrated in humans (cerebello-motor cortex inhibition) (Daskalakis *et al.*, 2004). Such a possibility would be consistent with the finding that patients with atrophy of the cerebellar cortex have enhanced LLSR (Diener *et al.*, 1984) that are reduced by applying anodal transcranial direct current stimulation in order to increase cerebello-motor cortex inhibition (Grimaldi and Manto, 2013). Moreover, electrophysiological tests supported the hypothesis that a decreased cerebellar drive from one hypoplastic cerebellar hemisphere caused abnormalities in the mechanisms which regulate transmission within M1 and that these, combined with abnormal somatosensory transmission, resulted in cortical myoclonus (Rocchi *et al.*, 2019) (Fig. 2).

The cerebellum is also known to be involved in the production of many types of tremor, together with M1. For instance, imaging and magnetoencephalography studies have shown that a cerebello-motor cortical loop is involved in the origin of essential tremor (Schnitzler *et al.*, 2009; Muthuraman *et al.*, 2018); physiological tremor can be modulated by phase-locked alternating current over the cerebellum (Mehta *et al.*, 2014); and parkinsonian tremor may also involve a cerebello-cortical loop controlled by the basal ganglia (Dirkx *et al.*, 2016). The existence of such loops could well be a factor in sustaining repetitive activity in cortical tremor and EPC. We propose that activity in these pre-existing loops reactivates focal discharges in the motor cortex resulting in regular muscle jerking (Rothwell, 1998; Hallett, 2014) (Fig. 2). Indeed, there is evidence for cerebellar abnormalities in several families with FCMTE (see below).

It is less clear how cerebellum is involved in EPC. EPC differs from cortical tremor in being localized and having a lower frequency around 1 Hz. Many authors consider it to be a focal motor status epilepticus (Mameniskiene and Wolf, 2017). Nevertheless, there are clear examples of cerebellar involvement such as a case of EPC following cerebellar

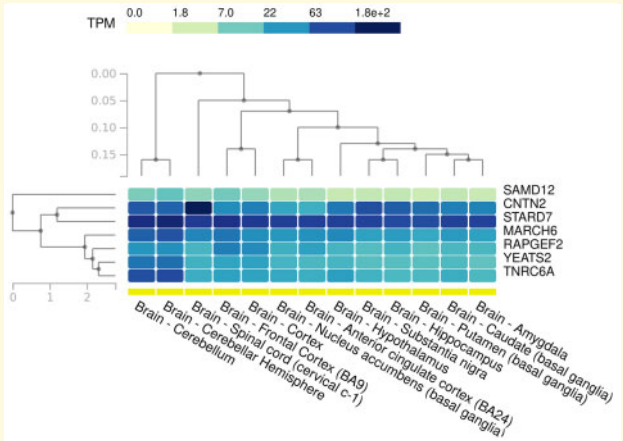

Figure 3 Expression patterns of FCMTE candidate genes in the brain. The heat map shows relative gene expression expressed as transcripts per kilobase per million mapped reads (TPM) based on the colour scale as shown. The data and image were obtained from: https://www.gtexportal.org, the GTEx Portal on 11/16/19. BA = Brodmann area.

haemorrhage and no evidence of cortical abnormalities (Vander *et al.*, 2004). The epileptogenic potential of the cerebellum remains elusive, although there is evidence supporting that seizure may also arise directly from it ('cerebellar seizures') (Foit *et al.*, 2017). Interestingly, the second most common seizure semiology in lesional cerebellar epilepsy is myoclonic seizures (Foit *et al.*, 2017).

Autosomal dominant familial cortical myoclonic tremor and epilepsy and the cerebellum

Strong evidence links non-coding repeat expansions with the pathogenesis of FCMTE, irrespective of the genes involved (Ishiura *et al.*, 2018). Exact pathogenic mechanisms remain unclear, but the transcription process appears key; expanded RNA aggregation-related neurotoxicity, translation of expanded RNA into neurotoxic peptides, or contributions to gain- or loss-of-function of related genes are possibilities (Todd and Paulson, 2010; Zhang and Ashizawa, 2017). Whether the genes identified share common features is still not known. However, many FCMTE genes are highly expressed in the cerebellum (Fig. 3). In FCMTE1, *SAMD12* encodes sterile alpha-motif domain-containing 12, a predicted intracellular protein of unknown function highly expressed in the frontal cortex and cerebellar hemispheres; RNA foci were observed in the cortical neurons and Purkinje cells in the brains of patients, which supports evidence that RNA-mediated toxicity is the mechanism underlying the pathogenesis of FCMTE (Cen *et al.*, 2018; Ishiura *et al.*, 2018). Moreover, neuropathological findings in patients with homozygous mutations in *SAMD12* showed mild and diffuse loss of Purkinje cells and halo-like amorphous material around the cytoplasm of several Purkinje cells (Ishiura *et al.*, 2018), similar to what was observed in patients with spinocerebellar ataxia (SCA) type 31, a pentanucleotide-repeat expansion disorder (Yoshida *et al.*, 2014). In FCMTE2 and in a Chinese pedigree, in which linkage to gene loci 8q24 or 2p11.1-q12.2 was excluded, magnetic resonance spectroscopy indicated cerebellar involvement (Striano *et al.*, 2009; Long *et al.*, 2016). FCMTE2 is caused by an intronic ATTTC expansion in *STARD7*; the same repeat expansion in intron 1 of *DAB1* is the cause of SCA37. Interestingly, both genes are highly expressed in the cerebellum. In a Dutch FCMTE3 pedigree, neuropathology showed severe Purkinje cell loss with dendritic sprouts, neuronal loss in the dentate nucleus and microglia activation, with limited changes in the sensorimotor cortex (van Rootselaar *et al.*, 2004, 2007; Sharifi *et al.*, 2012). Analogous pathological abnormalities have been found in one of the two cases of the South African FCMTE family described (Carr *et al.*, 2007). Finally, both *MARCH6* and *YEATS2* (related to FCMT3 and FCMT4, respectively) protein products are highly expressed in the cerebellum (Florian *et al.*, 2019).

Interestingly, FCMTE is one of three neurodegenerative disease caused by repeat expansion 'insertion', together with SCA31 and SCA37; the latter two are cerebellar diseases and have pathogenic/genetic similarities with some FCMTEs. These disorders might share pathological mechanisms, and the difference in gene expression, restricted to the cerebellum for the SCAs and broader for the FCMTE, may partly explain the different clinical phenotypes, and possibly the presence of epilepsy in FCMTE.

Conclusion

The core feature of FCMTE is cortical tremor, which is distinguished from other forms of cortical myoclonus by its rhythmicity. This feature, often making differentiation from other action tremors difficult, may be more than mere happenstance. We propose that a pre-existing cerebello-thalamo-cortical loop, which rhythmically synchronizes other tremors, provides feedback following a cortical discharge, reactivating the focus and resulting in sustained tremor.

One study identified bi-brachially coherent 8–9 Hz cortical tremor EMG bursts (Guerrini *et al.*, 2001), suggesting the presence of a pathway that synchronizes descending activity from motor cortices of both hemispheres. We propose that the cerebellum could be an integral node, as the inferior olive-cerebellar network is presumed to drive frequency oscillations of the neocortex (Welsh *et al.*, 1995; Ros *et al.*, 2009); alternatively, a common drive to descending activity could be located in the brainstem, as in orthostatic tremor (Antelmi *et al.*, 2018).

A clear notion emerges from our discussion, i.e. the pathophysiological importance of the cerebellum across the entire cortical myoclonus spectrum. Moreover, new genetic

evidence implicates intronic repeat expansions in a number of genes, highly expressed in the cerebellum in FCMTE; RNA toxicity is the candidate pathomechanism and cerebellar involvement might explain the presence of cortical tremor as main clinical feature. Future avenues to verify the role of the cerebellum in FCMTE could use a number of neurophysiological and neuroimaging techniques. For instance, the investigation of magnetic or electrical activity generated by the cerebellum is now viable (Pollok *et al.*, 2007; Todd *et al.*, 2018). It is also possible that in FCMTE a lack of cerebellar control of movement, which can be assessed with several experimental paradigms (Manto *et al.*, 2012), might be directly responsible for cortical tremor. This defective control might depend upon derangement in functional connectivity between the dentate nucleus and the contralateral M1, measurable by means of transcranial magnetic stimulation (TMS) (Galea *et al.*, 2009) or functional MRI (Gallea *et al.*, 2016). Ultimately, non-invasive brain stimulation techniques such as repetitive TMS or transcranial direct current stimulation, which have already been used to modulate cerebellar function (Di Biasio *et al.*, 2015; Monaco *et al.*, 2018), could be assessed as potential tools to induce changes in cortical tremor and, therefore, to indirectly verify the role of the cerebellum in its pathophysiology.

In conclusion, despite pathophysiologically being a form of cortical myoclonus, cortical tremor is phenomenologically a tremor, likely driven by the cerebello-thalamo-cortical loop. The cerebellum plays a role in its origin and could represent the link in the continuum of the cortical myoclonus spectrum; however, what determines the nature of neuronal discharges, and consequently the clinical picture, still needs to be determined.

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Competing interests

The authors report no competing interests.

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