A new familial disease of saccadic oscillations and limb tremor provides clues to mechanisms of common tremor disorders

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Tremor disorders pose fundamental questions about disease mechanisms, and challenges to successful neurotherapeutics: What causes motor circuits to oscillate in disorders in which the central nervous system otherwise seems normal? How does inheritance ‘determine’ the clinical phenotype in familial tremor disorders? Here, we address these questions. Analogies between the neural circuits controlling rapid eye movements (saccades) and those controlling limb movements allow us to translate the interpretations from the saccadic systems to the limb movement system. Moreover, the relatively well understood neurophysiology of the ocular motor system offers a unique opportunity to test specific hypotheses about normal and abnormal motor control of both eye and limb movements. We describe a new familial disorder—‘micro-saccadic oscillations and limb tremor (µSOLT)—in a mother and daughter who had tiny saccadic oscillations of the eyes and tremor of the hands. This unique oscillatory movement disorder resembles other common tremor disorders (such as essential tremor) that occur in patients who have an otherwise normally functioning central nervous system. We hypothesize that µSOLT is caused by an inherited abnormality that results in abnormal membrane properties causing reduced external inhibition in the premotor neurons that generate the high-frequency discharge (burst) for saccades and for ballistic limb movements. To test this hypothesis, we recorded hand tremor and eye movements in two patients with µSOLT and particularly during natural circumstances when inhibition of the premotor saccadic burst neurons is removed (e.g. eye closure). We then simulated a conductance-based model for the premotor commands which included excitatory and reciprocally inhibitory burst neurons. The structure of this physiologically realistic model was based upon known cell types and anatomical connections in the brainstem (for saccades) and the thalamus (for limb movements). The physiological phenomenon of post-inhibitory rebound in premotor burst neurons makes the circuit inherently unstable and prone to oscillate unless prevented by external inhibition. Indeed, with simulated reduction of external inhibition (in this case glycinergic), saccadic oscillations and limb tremor were reproduced. Our results suggest that a single-inherited deficit can alter membrane properties, which impairs inhibition in an inherently unstable neural circuit causing the eye and limb oscillations in µSOLT. This concept has broad implications for understanding the mechanism and designing rationale pharmacotherapy for abnormal oscillations and may be applicable to other common disorders in which there are no structural abnormalities in the brain such as essential tremor.

Keywords: ion channels; saccade; tremor; computational simulation; oscillations

Abbreviations: EBN = excitatory burst neurons; IBN = inhibitory burst neurons; IO = inferior olive; µSOLT = micro-saccadic oscillations and limb tremor; OPN = omni-directional pause neurons; PIR = post-inhibitory rebound; TC = thalamo-cortical; TR = thalamic reticular; VA = ventral anterior; VL = ventral lateral

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Introduction

Many tremor disorders, e.g. essential tremor and tremor with cervical dystonia, occur in a structurally sound central nervous system without any consistent patho-anatomical correlates. A similar situation often exists for tremor-like,
saccadic oscillations of the eye (unwanted, back to back saccades that occur upon one another, without an intersaccadic interval and disrupt clear vision) (Leigh and Zee, 2006). Saccadic oscillations may occur transiently in normal subjects, e.g. during eye closure, with convergence and sometimes they can be produced voluntarily (Ramat et al., 2005; Miura and Optican, 2006). Abnormal saccadic oscillations also occur, often dramatically, in patients with neurological disorders when they are called fluter or opsoclonus. Such pathological saccadic oscillations have been attributed to autoimmune (post-infectious and para-neoplastic) or various toxic and metabolic processes (Leigh and Zee, 2006).

We discovered a novel disorder of saccadic oscillations and fine hand tremor in a mother and her biological daughter who have had these symptoms since childhood. We call this novel disorder ‘familial micro-saccadic eye oscillations and limb tremor ($\mu$SOLT)’. Because the patients had no other ‘neurological abnormalities’, we assume their eye oscillations and tremor have a genetic basis and offer an analogy to other common familial tremor disorders such as essential tremor. Prior hypotheses to account for saccadic oscillations have had in common the idea that the instability arises from an abnormality in the feedback circuits that control the amplitude of saccades (Zee and Robinson, 1979; Wong et al., 2001). But these models do not explain the wide range of frequencies of oscillations that have been reported both for normal subjects (with a presumably normal nervous system) and patients with abnormal oscillations with an otherwise normally functioning central nervous system. Recently we have suggested different mechanisms to account for the appearance of saccadic oscillations in normal subjects, which allows oscillations of different frequencies to emerge depending upon changes in the properties of burst neurons themselves (Ramat et al., 2005). The key concept is that the instability arises because (i) brainstem inhibitory burst neurons (IBN) for agonist and antagonist muscles are reciprocally interconnected, providing an anatomical substrate for self-sustaining oscillations and (ii) burst neurons show post-inhibitory rebound (PIR), a spontaneous burst of activity after a neuron is released from sustained inhibition (Enderle and Engelken, 1995; Ramat et al., 2005; Miura and Optican, 2006).

Here, we study $\mu$SOLT using a ‘neuromimetic’ model of saccade generation in which (i) the circuit consisted of premotor excitatory, excitatory burst neurons (EBN) and IBN and their known anatomical interconnections, (ii) membrane kinetics were determined by specific subsets of membrane ion channels and (iii) reduction in external inhibition, glycnergic in the case of the saccadic system, lead to the appearance of saccadic oscillations during fixation and excessive rebound excitation after sustained inhibition (increased PIR). We then used a similar approach, based on an analogous central circuit within the thalamus that generates ballistic limb movements, to simulate their limb tremor.

Finally, this study presents a unique approach to study common tremor disorders such as essential tremor. Oscillations in the motor system in disorders like $\mu$SOLT or essential tremor pose fundamental questions about the mechanisms of disease in the motor system: What causes motor circuits to oscillate in the disorders in which the central nervous system otherwise seems normal? How does inheritance ‘determine’ the clinical phenotype in familial tremor disorders? Answers to these questions will influence the practice of clinical neurology and neurotherapeutics. We address some of these questions in the present study. The relatively well-understood neurophysiology of the eye movement system offers a unique opportunity to test specific hypotheses about normal and abnormal motor control. Moreover, analogies between the neural circuits controlling ballistic eye movements (saccades) and those controlling limb movements allow us to translate the interpretations from the eye movement systems to the limb movement system. Thus, the discovery of novel disorders of eye and limb movements such as $\mu$SOLT presents an opportunity to understand more common movement disorders, such as essential tremor of the head and limb in which there are no gross structural abnormalities within the brain.

**Methods**

**Eye movements and limb tremor recordings**

Both patients and healthy subjects signed appropriate consent material before enrolling in the study. The study was approved by The Johns Hopkins Institutional Review Board. Eye movements were recorded with the magnetic field/search coil technique in the adult patient and in healthy subjects. An infrared monitor (Ober saccadometer) was used to quantify the eye oscillations in the daughter. Limb tremor was recorded using three axis accelerometer (Tremormeter, FlexAble Systems, Fountain Hills, AZ).

For the mother, the movements of both eyes were recorded around all three axes of rotation (horizontal, vertical and torsional). The output signals of the coils were hardware filtered with a single pole RC filter with bandwidth of 0–90 Hz, and then sampled at 1000 Hz with 12-bit resolution. Readers are referred to Bergamin et al. (2001) for more details of the eye movement calibration and recording procedures. Tremor recording methodology is reviewed in detail in Caliguiri and Tripp (2004).

**Recording paradigms**

**Eye movements**

Three-dimensional eye positions were recorded as healthy subjects and patients with $\mu$SOLT fixed their gaze on the target of interest, closed their eyes, or made 20° and 40° saccades in horizontal and vertical directions.

**Hand tremor**

Hand tremor were recorded as subjects outstretched their arms (postural tremor), rested hands comfortably on the table in front of them (resting tremor) and attempted to reach an object of interest (kinetic tremor).
Results
The neurological phenotype of familial micro-saccadic oscillations and limb tremor (μSOLT)

The only symptoms of our patients were occasional brief episodes of blurring of vision, and hand tremor, both noted since early in childhood. The visual symptoms and hand tremor were accentuated during periods of stress or anxiety. The only neurological findings on simple visual inspection were intermittent brief bursts of eye oscillations and the hand tremor. For example, the video clip (see Supplementary material) of the daughter shows a brief burst of eye oscillations during otherwise normal smooth pursuit of the examiner’s finger. During ophthalmoscopy, however, both patients showed nearly continuous, small-amplitude, high-frequency oscillations of the eye. Neither patient showed abnormalities of saccades; they appeared to be generated promptly, and were accurate and fast. Quantitative recordings showed that the saccades made by the patients were of normal velocity and amplitude [for example, compare Fig. 1A (normal subject) and Fig. 1D (mother)]. During attempted steady fixation (Fig. 1E), however, there were nearly continuous, small-amplitude, high-frequency saccadic oscillations (≈18 Hz) around all three axes of rotation (horizontal, vertical and torsional) [compare with the normal subject (Fig. 1B)]. The daughter showed similar behaviour during fixation and the frequency of the saccadic oscillations was the same. Pursuit eye movements, convergence and vestibulo-ocular responses were normal. Both the mother (Fig. 1F) and daughter also showed a small-amplitude, high-frequency (≈12 Hz) tremor of their outstretched arms (postural limb tremor). A kinetic tremor was also present in both with a frequency of (≈11 Hz). The postural and kinetic tremors had similar amplitudes (postural: 18 mm/s² and kinetic: 18 mm/s²). There was no resting or head tremor.

Computational analysis of saccadic oscillations in μSOLT

We next develop a hypothesis to account for the saccadic oscillations of our patients. First, we discuss the key anatomical and physiological features of the neural circuits that underlie normal saccade generation, and then show how oscillations might emerge.

Normal generation of saccades

Sherringtonian reciprocal innervation—agonist excitation and antagonist inhibition—underlies the patterns of innervation to the ocular motoneurons for saccades. Three classes of neurons—excitatory burst neurons (EBN) within the pontine paramedian reticular formation, inhibitory burst neurons (IBN) within the rostral medullary reticular formation and omni-directional pause neurons (OPN) within the pontine raphe—comprise the premotor horizontal saccade circuit (Fig. 2). For example, when we want to make a rightward saccade, premotor neurons on the right side of the brainstem send excitation to motor neurons for rightward saccades and send inhibition to motor neurons for leftward saccades (Fig. 2A, green lines are excitatory, red lines are inhibitory neurons, grey lines are inactive neurons). When we are not making saccades, the EBNs and IBNs on both the left and right are held off by tonic glycnergic inhibition from the OPN. Each OPN pauses for saccades in all directions. Removal of OPN inhibition at the initiation of the saccade allows a high-frequency burst of neuronal activity in the premotor burst neurons to drive saccades (Ramat et al., 2007). Part of the burst following the silencing of the OPN discharge reflects a ‘rebound’ increase in neural activity after transient inhibition and is thought to be due to PIR (Enderle and Engelken, 1995; Ramat et al., 2005; Miura and Optican, 2006). Projections from the IBNs on the right side inhibit EBNs on the left, and vice versa, also through glycnergic transmission (Horn et al., 1996). We proposed that these connections form a ‘short-latency, mutually inhibitory’ circuit between the left and right sides that is inherently unstable (Ramat et al., 2005).

How saccadic oscillations might appear in normal subjects

How does mutual inhibition between neurons with PIR lead to network oscillations? Figure 2B schematizes a neural circuit formed by two mutually inhibitory neurons (neuron-A and -B). Suppose a small increase in neural activity, either from spontaneous fluctuation (noise) in neural activity or a small spontaneous saccade, causes a brief pulse of activation (dashed line) that starts neuron-A firing. When neuron-A discharges, it inhibits neuron-B. After the input to neuron-A ceases, its discharge drops, removing the inhibition from neuron-B. Neuron-B, in turn shows a PIR increase in its firing rate. After neuron-B inhibits neuron-A, the same PIR occurs in neuron-A. Thus, PIR in reciprocally inhibited neurons is enough to cause oscillations (Fig. 2C). These oscillations are normally prevented by tonic glycnergic inhibition from the OPNs. If the activity of OPN could be diminished physiologically in normal subjects they might show transient saccadic oscillations. In fact, OPN activity is diminished naturally when normal subjects close their eyes (Fig. 3A), combine vergence with a saccade (data not shown) or make pure vertical or pure horizontal saccades (Fig. 3B). In the last case, for example, a large horizontal saccade is accompanied by (vertical) saccadic oscillations in the orthogonal direction since different sets of burst neurons generate horizontal and vertical saccades but all OPN cease discharging for saccades in all directions. These experimental results suggest that instability in the saccadic burst generating system, introduced by the removal of OPN inhibition, is the cause of saccadic oscillations in normal subjects.
**Fig. 1** Saccades in patients with familial \( \mu \text{SOLT} \) are normal in speed and accuracy [compare normal subject (A) and patient (D)]. Gaze holding in patients with \( \mu \text{SOLT} \) is also normal (D). During attempted steady fixation there are micro-saccadic oscillations in the patient [compare E and B (normal subject)]. Hand tremor is seen in patients with outstretched hands (postural limb tremor) (F), but not in the normal subject (C).
Following on the idea that a decrease in OPN inhibition leads to saccadic oscillations, we developed a hypothesis to explain the abnormal saccadic oscillations in our patients. We propose that a single deficit (such as, reduction of the conductance of the strychnine-sensitive glycine channel) could change the properties of the burst neuron membrane resulting in reduced inhibition of this circuit by the OPNs and making the neural network oscillate, even when steady fixation is desired. In other words, we are suggesting that the defect here is a ‘channelopathy’ in which there is a deficit in the ability of the glycine channel to conduct chloride ions—i.e. reduced glycinergic conductance.

Simulations of saccadic oscillations in normal subjects and in μSOLT

To address this hypothesis quantitatively, we simulated a conductance-based single-compartment model of burst neurons within a local feedback loop model of the saccadic system (Miura and Optican, 2006). The general schema for the major conductances is shown in Fig. 4. The mathematical details of the simulation are detailed in the Appendix. Using normal membrane properties and a normal profile of expression of ion channels the model simulated behaviour in normal subjects with stable fixation with eyes open, normal amplitude and velocity saccades, and by turning off the OPN, saccadic oscillations (comparable to Fig. 3A, during eye closure). The pathological oscillations of μSOLT were simulated by reducing the chloride conductance through the strychnine-sensitive glycine channel of the model premotor burst neurons. The model simulated small-amplitude saccadic oscillations during fixation with eyes open. As expected the saccades themselves remained normal (Fig. 5A and C). The model also simulates oscillations during eye closure (Fig. 5B) and oscillations in the orthogonal direction during horizontal or vertical saccades (Fig. 5C).

One important difference was noted between the behaviour of the patients and that of the normal subject. The amplitude of the oscillations in the patient was larger than in the normal subject during eye closure and along the orthogonal axis during large purely vertical or horizontal saccades. In addition, during saccades and eye closure, the amplitude of the oscillations in the patient increased above
that during fixation. Our simulations also showed this behaviour because the pathologically decreased glycinergic inhibition reduces the level of hyperpolarization of the burst neuron membrane, which reduces the threshold for neural firing. This, in turn, leads to increased membrane excitability and thus an increased strength of PIR. Therefore, during attempted steady fixation, although OPNs are turned on, there is decreased effect of glycinergic inhibition on the burst neurons and micro-oscillations occur. Furthermore, the increased membrane excitability and reduced threshold results in pathologically amplified effects of turning off the OPNs resulting in an increased amplitude of oscillations during orthogonal saccades and eye closure.

**Computational analysis of limb tremor in μSOLT**

**How do we explain limb tremor in μSOLT?**

Limb tremors are traditionally thought to arise from oscillation in central neurons or from mechanical abnormalities in the reflex-arc. The similar frequency and amplitude of kinetic and postural tremor in our patients suggest a central origin for the limb tremor in μSOLT. There are at least two possible mechanisms, not necessarily mutually exclusive, underlying oscillations in the central
neurons generating limb movements; one may reside primarily in ‘olivo-cerebellar’ circuits and the other in ‘thalamo-cortical’ (TC) circuits.

**An olivo-cerebellar mechanism for tremor**

One mechanism for tremor is that a group of neurons within a single nucleus develops an abnormal oscillatory mode. In this mode, a neural discharge is followed by a prolonged hyperpolarization which then terminates in rebound spikes. Thus, each neuron oscillates independently. Synchronization of such independently oscillating neurons could result in rhythmic activity that becomes strong enough to cause gross motor oscillations. Electrotonic coupling through connexin gap junctions can facilitate such synchronization in premotor nuclei such as the inferior olive (IO) (Sotelo et al., 1974). Cells of IO also express ion channels that carry $I_{H}$ (hyperpolarization activated cation current) and $I_{T}$ (low-threshold calcium current). Moreover, $I_{H}$ is thought to influence the synchronization of oscillations in IO (Bal and McCormick 1997). Octanol, which reduces synchronized oscillations in IO, also reduces essential tremor (Sinton et al., 1989; Shill et al., 2001). Glycinergic inhibition to IO is sparse, yet present (De Zeeuw and Berrebi 1995). Therefore, impaired glycineric inhibition resulting in increased PIR (as explained earlier) could cause increased synchronized oscillatory behaviour in IO manifesting as limb tremor in μSOLT.

**A thalamo-cortical mechanism for tremor**

The mechanism presented earlier, which is based on electrotonic conduction within the IO, cannot easily explain the saccadic oscillations of our patients. So, we invoked a second possible mechanism for tremor: increased instability due to reduced ‘external’ inhibition in a neural circuit.
characterized by reciprocal innervation. We then asked if there might be a comparable circuit for limb movements to that for eye movements that would be susceptible to and produce limb oscillations. Reciprocal innervation is also noted in spinal as well as more central neurons controlling limb movements (Sherrington, 1907). The globus pallidus internus (GPI), sends inhibitory GABAergic projections to the motor thalamus [ventral anterior (VA) and ventral lateral (VL) thalamic relay nuclei], which relays the output to the motor cortex [Parent and Hazrati, 1995]. The thalamus may participate in the generation of limb movements similar to the way the brain stem reticular formation generates premotor commands for saccades. TC relay neurons send glutamnergic excitatory projections to the thalamic reticular (TR) neurons (as EBNs send excitatory projections to contralateral IBNs in the oculomotor system). The TR neurons also have inhibitory feedback projections to TC neurons (as IBNs send inhibitory projections to EBNs). TR neurons mutually inhibit each other (as IBNs mutually inhibit each other across the midline) [Takada and Hattori, 1987; Sherman and Guillery, 2001; Guillery and Harting, 2003; Pinault, 2004]. The globus pallidus (GP) sends inhibitory projections to TC and TR neurons which could be analogous to OPN-induced inhibition of the saccadic burst neurons. Inhibitory neurotransmitters of the GP system are GABA and glycine [Takada and Hattori, 1987]. Furthermore, thalamic relay and GPI neurons also exhibit PIR (Llinas and Jahnsen, 1982; Nambu and Llinas, 1994). Hence, analogous to the neural circuit formed by the premotor neurons of the saccadic system, a neural network formed by the TC and TR neurons for controlling limb movements is also reciprocally inhibitory and might also be inherently unstable, and physiologically under control by external inhibition. Therefore, we propose that similar mechanisms—impaired external inhibition upon an inherently unstable circuit that normally generates reciprocally innervated movements—underlie limb tremor in familial SOLT.

A conductance-based model of thalamic burst neurons simulates limb tremor

A conductance-based computational model of thalamic burst neurons was simulated to generate limb tremor. While the circuitry and structure of this model was analogous to that for generating saccades there are key differences between the two models in the expression profile of different subtypes of ion channels carrying hyperpolarization activated cation current ($I_{H}$). For limb tremor, the expression profile of the simulated ion channel subtypes carrying $I_{H}$ conductance was made consistent with the presumed profile in TC and thalamic relay neurons [Monteggia et al., 2000]. This model simulated the hand tremor and had a similar frequency to that observed in the patient (Fig. 3E). Note the considerable difference between the frequency of oscillations of the hands (12 Hz) and eyes (18 Hz) in our patients (Fig. 5E).

Discussion

Impaired inhibition in inherently unstable neural circuits generating rapid ballistic movements

Here, we report a novel familial disorder characterized by tiny saccadic oscillations with hand tremor. The symptoms began early in the life and were not associated with any known acquired cause of eye oscillations such as toxic, metabolic, infectious or immune-mediated disease. This suggests an inherited origin. We attribute the saccadic and limb oscillations in this familial disorder to an unmasking of the inherent instability associated with reciprocally inhibitory premotor neural circuits that underlie reciprocal innervation of agonist–antagonist muscle pairs.

We simulated micro-saccadic oscillations with a membrane-based model of premotor burst neurons innervating agonist-antagonist muscle pairs. The key features of this model are PIR and the inherent instability of the burst neuron circuit which results from reciprocal inhibition between the neurons that innervate agonist and antagonist muscle pairs. The model reproduced micro-saccadic oscillations when glycinergic inhibition of this circuit was reduced.

We speculate that thalamic circuits relaying signals related to ballistic limb movements may be functionally analogous to the premotor saccadic burst generator. We emphasize that we know much less about the direct, premotor contribution of thalamic circuits to the generation of limb movements than we know about the circuits that generate the premotor commands for saccades, but we think it likely that similar principles underlie the generation of ballistic limb movements. Therefore, the same pathological deficit—removal of external inhibition from mutually inhibitory circuit might also explain the limb tremor in our patients. Using a slightly different, but physiologically plausible, set of ion channel kinetics than used to simulate saccadic oscillations, the same simulated membrane deficit—reduced external inhibition of reciprocally innervating neural circuits—reproduced the characteristics of limb tremor.

Why do eye and limb oscillations have different frequencies?

There was a considerable difference in the frequency of the eye oscillations and the limb tremor (18 and 12 Hz, respectively). This difference in frequency is likely related to differences in the central and peripheral mechanisms responsible for eye versus limb movements and to the mechanical properties of the eye and limb (the motor ‘plant’). For example, (i) there is no stretch reflex in the extra-ocular muscles [Keller and Robinson, 1971], but there
is in the limbs, (ii) the dynamics of the limb motor ‘plant’ (i.e. the physical properties of the muscles and connective tissues in the limbs) are different between the eye and limbs. It is possible that the relatively larger mass of the fingers and hand is associated with a lower-frequency physiological and an enhanced physiological mechanical-reflex tremor. The hand tremor in our patients, however, was presumably of central origin, and its frequency therefore would not be affected by limb inertia. Unfortunately, we could not study the limb tremor in our patients with mass loading, as described by Deuschl et al. (2001).

For the purposes of our simulations we optimized the mechanical time constants in the simulated limb motor ‘plant’ according to the tremor of our patient. Another important factor in determining both the amplitude and the frequency of oscillations could be the strength of PIR. The expression pattern of ion channel subtypes carrying hyperpolarization-activated cation currents ($I_{\text{H}}$) and low-threshold calcium currents ($I_{\text{T}}$) determines the membrane kinetics and thus the strength of PIR (Llinas, 1988; McCormick and Pape, 1990; Sekrjnak and du Lac, 2002; Nelson et al., 2003; Perez-Reyes, 2003). Indeed a simulated increase in activation of $I_{\text{T}}$ and/or $I_{\text{H}}$ changes the frequency and amplitude of the oscillations (Fig. 6). In particular, a stronger $I_{\text{T}}$ simulates a larger oscillation amplitude, whereas a stronger $I_{\text{H}}$ simulates a higher oscillation frequency. The relative pattern of expression of the four subtypes of ion channel carrying $I_{\text{H}}$ can also influence the oscillation frequency. A larger proportion of $I_{\text{H}}$ channel subtype with the shortest activation kinetics (HCN1) causes a higher frequency of oscillation. On the other hand, a larger proportion of the $I_{\text{H}}$ subtype with the longest activation kinetics (HCN4) causes a lower frequency of oscillation. Compared to thalamic burst neurons, the premotor saccadic burst neurons presumably have a relatively larger proportion of $I_{\text{H}}$ channel subtypes with faster activation kinetics (Montegaglia et al., 2000). In addition, inherent synaptic delays associated with the feedback loops from motor neurons to premotor neurons could also contribute to differences in frequency between the eye oscillations and the hand tremor.

In spite of the many possible differences between the neural networks that generate eye and limb movements, and the differences in the effector organs, we suggest a common pathophysiology for oscillations in these networks in our patients: a reduced efficacy of the external inhibition on the premotor burst neuron networks that generate eye and hand movements. The differences in the membrane ion channel kinetics expressed in different neurons (here thalamic burst neurons and pontine burst neurons) is an important factor in determining the different frequencies of eye and limb oscillations.

**An approach to study more common tremor disorders such as essential tremor**

This combined clinical, biophysical and computational approach to a rare disorder of the ocular motor system may have broader implications for understanding the pathophysiology of and developing rational therapies for abnormal oscillations in other motor systems. Essential tremor, tremor associated with dystonia and the rapid saccade-like head oscillations that are sometimes associated with saccadic eye oscillations might have origins in altered membrane properties related to neurons that burst during head, eye and limb movements. We suggest that, on the one hand, oscillations in these other motor systems might be caused by reducing the effect of inhibitory input, either on an acquired (toxic or immune mediated) or on an inherited basis. On the other hand, the specific complement of ion channel subtypes may determine the characteristics of the oscillations. This, too, would be under genetic control and might explain why there is a wide range of frequencies of saccadic oscillations across normal individuals (Ramat, et al., 2005) but within a family of normal subjects (including our family), the frequency of saccadic oscillations is almost the same (Neppert and Rambold, 2006).

While these hypotheses remain to be proven, they nevertheless suggest new genetic, experimental and clinical approaches to disorders of movement, and especially those in which there are no gross structural abnormalities within the brain. Treatment with pharmacological blockers targeted towards these ion channels may offer therapeutic benefits. For example, although counterintuitive, interfering with the function of a normal ion channel to decrease membrane excitability in the face of impaired external inhibition might reduce oscillatory behaviour. Such an approach is similar to that for inherited epilepsy when seizures presumably are caused by an abnormal ion channel, while treatment targets another, presumably intact channel (Cannon, 2006). Indeed, propranolol—a commonly used beta-blocker that reduces membrane excitability (McCormick and Pape, 1990) is an effective drug for treating essential tremor (Gilligan, 1972). Alternatively, enhancing the function of an impaired ion channel might also reduce oscillatory behaviour. For example, ethanol, which enhances the conductance through the glycine channels, ameliorates essential tremor (Eggers and Berger, 2004).

**Supplementary material**

Supplementary material is available at **BRAIN** online.

**Acknowledgements**

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Oscillations occur in the model after reducing glycinergic inhibition. The frequency of the oscillations is determined primarily by the kinetics of the $I_H$ and $I_T$ currents, which in turn depend upon the distribution of ion channel subtypes (upper panels). Kinetics of the four $I_H$ subtypes have a 1.5-fold range, thus the frequency depends on the proportion of each subtype expressed in the burst neurons. Saccadic oscillations involve pontine burst neurons, which express more of the subtypes of $I_H$ channels with faster activation kinetics (Monteggia et al., 2000). This contributes to the higher frequency of saccadic oscillations. Limb tremor may involve thalamic burst neurons, which express a larger proportion of the slower $I_H$ channel subtypes (Monteggia et al., 2000). This contributes to the lower frequency of limb tremor. The amplitude of the oscillations depends primarily on the maximal conductance through $I_T$ channels (lower panels). Black, grey and white asterisk indicate the values of $I_H$ and $I_T$ maximal conductances used in the simula.

References

Appendix

Computational simulations

The Hodgkin–Huxley equations were implemented to simulate action potentials. A glycine channel was implemented for inhibition, and non-NMDA and NMDA channels for excitation. CaV3 channels for inhibition, and non-NMDA and NMDA channels for excitation. CaV3 channels (carrying $I_{Na}$) and four subtypes of HCN channel (HCN1–HCN4) were included to simulate PIR and to modulate the effectiveness of glycnergic inhibition. Not the activation kinetics of subtypes of ion channels carrying $I_{Na}$ are significantly different from each other, HCN-1 being the fastest and HCN-4 the slowest, with the others in between, as reflected in their activation time constants (Monteggia et al., 2000).

The following equation describes the time evolution of the membrane potential of the brain stem neurons:

$$C \frac{dV}{dt} = -I_L - I_T - I_{Na} - I_K - I_{Gly} - I_{GluNMDA} - I_{GluNonNMDA} - \sum_{j=1}^{4} \eta_j I_{Hj}$$  (1)

where, $V$ is the membrane potential of the burst neuron, $C$ is the membrane capacitance ($1 \mu$F/cm²) and $\eta_j$ is an expression rate scaling factor determining the ion channel expression profile in the burst neuron. $I_L$, $I_T$, $I_{Na}$, $I_K$, and $I_{Gly}$ denote the leak current, low-threshold calcium current, hyperpolarization activated current (carried by HCN1–4), fast sodium current and delayed rectifier potassium current, respectively. $I_{Glu}$ and $I_{Glia}$ are synaptic currents mediated by glycnergic and glutamatergic (NMDA and non-NMDA type) synapses. Details of these currents are presented in Miura and Optican (2006). This model added one new channel type, for the HCN currents. The equations for $I_{Hj}$ are:

$$I_H = g_{Hj}(V - E_H)$$  (2)

$$\frac{dx}{dt} = \frac{\lambda (x - a)}{\tau}$$  (3)
\[ \alpha(V) = \frac{1}{1 + \exp\left(\frac{V - V_0}{\theta}\right)} \quad (4) \]

\[ \tau(V) = 0.01 + \frac{1}{\exp[-14.59 - 0.086 V] + \exp[-1.87 + 0.0701 V]} \quad (5) \]

where, \( g_H = 9 \text{ mS/cm}^2 \) and \( E_H = -40 \text{ mV} \) denote the maximal conductance and the reversal potential of this channel, respectively (citation). The four different HCN channels are determined by the parameters in the Table 1 (Moosmang et al., 2001):

<table>
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