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The onset of voluntary reactive movement is temporally influenced by the central oscillation in action tremor caused by multiple sclerosis

Michael F.K. Wong[a], R. Christopher Miall[b], Peter G. Bain[a], Xuguang Liu[a,*]

[a] The Movement Disorders and Neurostimulation Unit, Department of Clinical Neuroscience, Division of Neuroscience and Mental Health, Imperial College London & Department of Neuroscience, Charing Cross Hospital, London, UK
[b] Behavioural Brain Sciences, School of Psychology, University of Birmingham, Edgbaston, Birmingham, UK

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ABSTRACT

The influence of oscillatory activity in the motor system on the generation of voluntary movement has been previously studied by revealing temporal coupling between voluntary movements and associated physiological or pathological tremor. The present study aims to investigate whether there is any temporal correlation between the onset of a rapid reactive movement and the action tremor at the wrist in patients with multiple sclerosis (MS).

In 13 MS patients, their reactive wrist movements and tremor were simultaneously recorded during a visually cued simple reaction time task. Significant correlation was found between the tremor-related and non-tremor-related measurements of the wrist movement. The onset of reactive movement was unevenly distributed over the tremor cycle peaking at 177° in the direction opposite to the reactive movement, suggesting a temporal coupling between the reactive movements and tremor. No significant difference in reaction time was found between voluntary flexion and extension movements, and no significant differences in the mean values or the standard deviations of the reaction time between the movements in-phase and out-of-phase with tremor were detected, suggesting that entrainment of the spinal motor neurons is not influenced by tremor activity.

In conclusion, in MS action tremor, the timing of the initiation of a rapid voluntary movement may be influenced by the pathological oscillator at a supra-spinal level.

There has been a long-term interest in the influence that oscillatory neural activity in the central nervous system (CNS) may have in motor control. Early evidence from neurophysiological studies in animals confirmed that the discharges of the cortical motor neurons synchronizes at certain preferred frequencies [10]. Further efforts have been made to find convincing evidence for an interaction between central oscillations and the generation of voluntary movements. In human studies, one approach has been to study subjects who have either physiological or pathological tremors which are thought to be driven essentially by oscillatory activity in the CNS, with or without the peripheral distortion and magnification (for a review, see [9]). One of the key points of focus is the temporal relationship between pathological tremor-related central oscillation and the timing of the initiation of voluntary movement. Tremor is often perceived as a source of unwanted noise in the system, and if so tremor oscillations cannot help, even indirectly, to make the motor performance faster or better [3].

However, some studies on physiological [6] and pathological tremors [12,4] have suggested that there is a functionally significant effect of tremor on the initiation of voluntary movements and asked whether the onset of voluntary movement is temporally influenced by the activity of a central oscillator. Other studies looking at the phase relationship between physiological tremor and the voluntary initiation of movement have tended to support a mechanistic relationship between them. Goodman and Kelso [5] demonstrated, in a rapid voluntary finger movement task, a "clear and systematic relationship between tremor and movement initiation" and that those movements were "initiated when the muscle-joint system possessed peak momentum" [5]. Analogous results were established by Wierzbicka et al. [12] in pathological Parkinsonian tremor, and they observed that "voluntary contraction is not initiated arbitrarily with respect to tremor oscillation".

* Corresponding author at: 10th floor, Laboratory Block, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK. Tel.: +44 2088467631; fax: +44 2083830663.
E-mail address: x.liu@imperial.ac.uk (X. Liu).

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Elble et al. [4] also obtained similar results in essential tremor. A recent study, however, has demonstrated little or no phase relationship between tremor and the initiation of voluntary movement: Lakie and Combes [6] showed no simple temporal relationship between the initiation of rapid reactive wrist movements and the phase of an enhanced physiological tremor in man and concluded that the central or spinal mechanism generating this tremor does not gate the central mechanism that produces voluntary movement.

In multiple sclerosis (MS), action tremor of the arm is the major form of movement disorders which are estimated to appear in 50% to 75% of patients. MS, consequent to cerebellar dysfunction, causes various types of action tremor that vary from mild to extremely severe [1]. The most severe forms of arm tremor in MS are proximal, causing tremor at the shoulder and are associated with the highest tremor-related disability scores, followed in decreasing order of disability by distal postural/kinetic tremor, isolated intention tremor, and finally distal postural tremor, the latter producing no disability [1]. Amongst pathological tremors, MS tremor may be caused by the stronger types of pathological oscillation associated with higher disability scores because of either significant involvement of proximal arm joints or high tremor amplitude compared to the less disabling distal and low amplitude arm tremors seen in Parkinsonism and physiological states. In parallel to assessing MS tremor as a means of identifying patients who could most benefit from surgical treatment [7], the present study aims to investigate if there is any temporal correlation between the onset of a rapid reactive wrist movement and the tremor oscillation in patients with MS. We simultaneously recorded voluntary reactive movements of the wrist and action tremor using a previously reported visually cued reaction paradigm [8]. We hypothesised that if the onset of the reactive movement was temporally coupled with the action tremor, then the onset of the reactive movement measured as reaction time (RT), a non-tremor-related measure, would significantly correlate with the phase values of the tremor cycle, a tremor-related measure. Furthermore, if entrainment of the spinal motor neurons responsible for initiating voluntary movement is influenced by descending tremor activity driven by a central oscillator, then the RTs involving flexion and extension of the wrist, and movements initiated in-phase and out-of-phase with the tremor cycle will be different.

Performance of the simple reaction time task was recorded from 13 MS patients with action tremor (6 females and 7 males with a mean age of 36 years (21 to 52 years)). Patients were either outpatients at the Department of Neurology or inpatients at the Department of Neurosurgery, Radcliffe Infirmary, Oxford. All patients had been diagnosed as having either clinically definite MS or laboratory-supported definite MS according to the MS classification of Poser et al. [11]. Patients with clinically detectable visual or oculomotor defects were excluded from the study. All patients had sustained tremor at both rest and action with severity ranged from 3 to 6 in a 10-point scale [2], and the tremor frequency ranges from 2.8 to 4.5 Hz among patients on the power spectra. Tremor, not ataxia, in each of the patients was identified based on the existence of a sharp spectral peak over slow ramp-tracking movements [8].

The visually cued simple reaction time task has been previously described in detail [8], and is summarised here (Fig. 1a): The patient was seated in a chair with the testing forearm supported at waist level, and strapped in place by a fixed adjustable plastic channel. This permitted unrestricted wrist flexion and extension movement over a range of 60° around its neutral position in the horizontal plane, whilst minimising the possibility of a simple mechanical linkage between the tremors observed in the tested wrist and the ipsilateral shoulder or the contralateral hand. Displacement of the

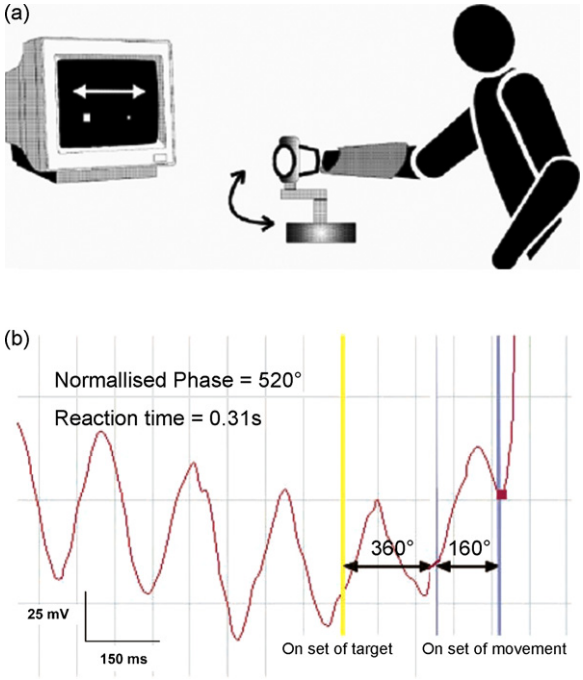

Fig. 1. (a) A diagram of the visually cued reaction time task. A hollow square jumps across the screen at random intervals. The patient was instructed to rotate a low-friction joystick by a wrist flexion or extension movement in response to the jumping target. The forearm was supported in an adjustable plastic channel, set for each subject in order to hold the forearm firmly whilst allowing comfortable wrist flexion and extension over a range of 60° (±30° around the neutral position). (b) A representative recording from a female patient aged 45. The onset of reactive wrist movements was measured in two ways with reference to the onset of a visual cue displayed on the screen: (1) a non-tremor-related measure: reaction time in seconds, and (2) a tremor-related measure: phase value in degrees.

hand was recorded continuously by a low-resistance hand-held potentiometer. The voltage signal generated by the joystick was amplified and digitally sampled with 12-bit resolution at 70 Hz. The patients were shown a square visual target (100 × 80 pixels) displayed on a VGA computer screen. The target jumped from one side of the screen to the other side at random intervals of 2–4 s. The patients were instructed to move the joystick as fast as possible upon the movement of the target, and to move explicitly in the direction of the target, without worrying about the magnitude or accuracy of the movement. Visual feedback of wrist movement was not provided throughout the task.

Tremor and reactive movement data were processed using MATLAB (MathWorks Inc.), and exported to Excel for further analysis and statistical testing. Data were analysed in terms of the number of tested hands rather than the number of patients as: (1) each hand was tested separately with restriction on possible mechanical contamination from the contralateral arm; and (2) it was previously shown that the tremors in the hands were statistically independent of each other [8].

The average frequency of the tremor cycle for each trial was computed by taking the mean of several measurements of the instantaneous frequency throughout the trials. The instantaneous frequency was calculated from the reciprocal of the interval (period) between two successive peaks in the tremor cycle (frequency = 1/period). The peak-to-peak values were measured manually by means of a cursor. To avoid ambiguity between tremor and ataxic movements and improve the reliability of measurements, these were only made where clear and sharp tremor peaks were present, as ataxic movements were less rhythmic than oscillatory tremor. A mean frequency that was representative of the tested

hand was then derived from the average frequency taken over 8 trials.

The onset of the reactive movement was measured in two ways (Fig. 1b). Firstly, it was measured as reaction time, a non-tremor-related measurement, as the time interval from the onset of the target movement to the onset of wrist movement. As the reactive movement and action tremor were superimposed in the record, the onset of reactive movement was identified in each trial as the point where there was a sudden change in the smooth tremor oscillation with either a reversal in movement direction or a sudden increase in movement velocity from the smooth oscillatory pattern. The instantaneous velocity profile was derived by differentiating the position signal. The mean RT of the hand was then calculated over 8 trials and in addition the mean RT was computed separately for wrist flexion and extension movements. Secondly, the onset of the reactive movement was measured in terms of the phase value of the tremor cycles, a tremor-related measurement. This was estimated as the number of tremor cycles $\times$ 360° between the onsets of the visual cue and reactive movements. The phase value was calculated for each trial, and the mean value across 8 trials was used to represent the phase value of that hand. Two measurements of the reactive movement were correlated and statistically tested.

If the onset of reactive movement occurred in the direction of movement of the tremor cycle, it was classified as in-phase. It was classified as out-of-phase if the onset of movement was in the opposite direction to the movement of the tremor cycle. Trials, estimated to be about 10–15% of the total number of trials, in which movements were initiated whilst the tremor movement was neither in the same nor in the opposite direction of the intended movement were excluded from the in-phase and out-of-phase movement comparisons. The reactive movements of each hand were grouped into those in-phase and out-of-phase with tremor, and the mean values of these two groups were compared using unpaired *t*-test.

The time interval from the last tremor peak to the onset of voluntary movement was evaluated for all recorded trials and represented in a frequency histogram over all 21 tested hands. The mean phase of the onset of the voluntary movement was calculated.

A clear tremor-dependent effect on the RT by the phase values of the voluntary movement onset was confirmed by the differential correlations of the RT with the phase measurements and with the tremor frequency: no significant correlation was found between RT and tremor frequency ($n = 21$, $r^2 = 0.07$, $p > 0.2$), whereas a significant correlation appeared between the phase values and tremor frequency ($n = 21$, $r^2 = 0.33$, $p < 0.007$).

The most interesting result was that there was a statistically significant correlation between RT and the phase values of the reactive movement onset ($n = 21$, $r^2 = 0.38$, $p < 0.003$; Fig. 2). The onset of the voluntary movement was distributed unevenly over the tremor cycle with a mean onset value of 177° (±91.78°), suggesting that the onset of voluntary movements was more likely to occur at a particular phase of the tremor cycle, notably when tremor reached its peak in the opposite direction to the reactive movement (Fig. 3). Furthermore, there was no significant difference in RTs of the flexion and extension wrist movements (unpaired *t*-test; $n = 21$, $p > 0.5$), and the correlation between the RTs in flexion and extension was highly significant ($n = 21$, $r^2 = 0.73$, $p < 0.000001$). No significant difference was found in both the mean value and the standard deviation of the RTs between movements in-phase and out-of-phase with tremor.

Based on previous studies of pathological tremors, such as Parkinson's disease [12], and essential tremor [4], where the timing of voluntary movement is linked to the phase of the tremor cycles,

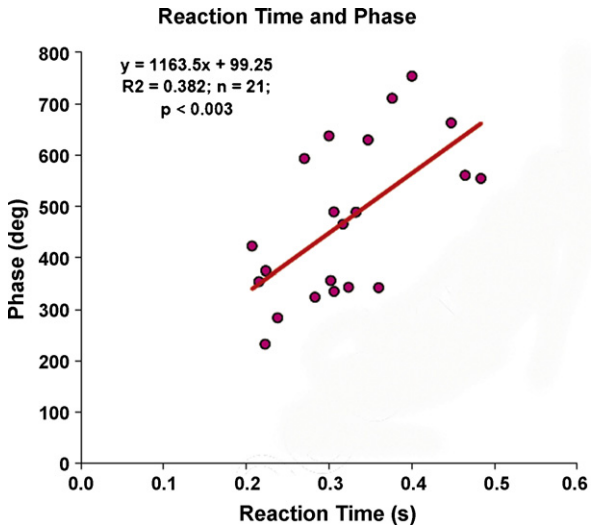

Fig. 2. Significant correlation between the non-tremor-related and the tremor-related measurements of the movement onset: reaction time and phase value.

it was anticipated that temporal coupling would exist between the onset of voluntary movement and tremor oscillations in MS action tremor. In contrast to various pathological tremors, no such temporal coupling was found in studies on enhanced physiological tremors [6]. Taken together, it seems reasonable to speculate that the temporal coupling between involuntary tremor and voluntary movement may in fact depend highly on the nature of the tremor oscillation, i.e. a temporal coupling is more likely to occur in the presence of stronger types of pathological oscillation resulting tremors associated with higher disability scores due to either significant involvement of proximal arm joint or high tremor amplitude, such as essential tremor and more so MS tremor, compared to the weaker Parkinsonian and physiological tremors. In other words, perhaps, it is no incidental that essential and MS tremors are generally considered to be cerebellar in origin whilst PD and physiological tremors are not.

Although it is not yet known whether MS tremor is driven by agonist (extensor or flexor only) or antagonist (extensor and flexor) activity, our findings indicate that there was no difference in RTs between rapid flexion and extension movements of the wrist, and more importantly no difference between RTs that were in-phase and out-of-phase with tremor. This suggests a supra-spinal origin for MS action tremor, and perhaps, MS tremor is driven by both flexor and extensor activity. Entrainment of the spinal motor neurons is not influenced by tremor activity and no mechanical advantage in term of energy efficiency appears when the voluntary movement occurs in the same direction as that of the tremor cycle. In fact, our results show that the onset of the reactive movement occurs when the tremor reached its peak in the opposite direction to the voluntary movement. These results provide further evidence to support a general theory [9] that pathological tremors of the limbs may actually be the direct results of derangement of central oscillators.

In conclusion, in MS tremor, the onset of voluntary reactive movement is temporally influenced by action tremor, and such functional coupling suggests that the timing of the initiation of a rapid voluntary movement may be influenced by the pathological oscillator at a supra-spinal level within the central nervous system. The onset of the voluntary movement occurs against potential mechanical advantage, and the entrainment of the spinal motor neurons between antagonist pools is not influenced by tremor activity.

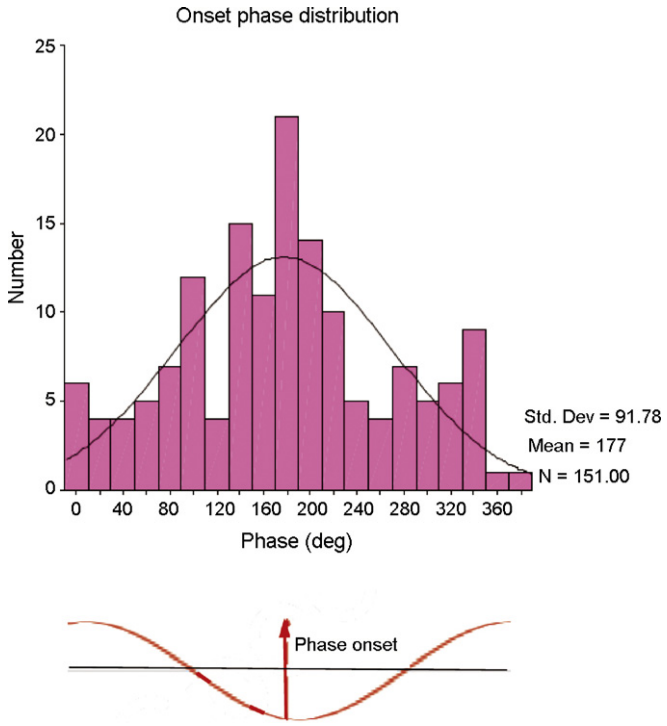

Fig. 3. The onset of reactive movement is unevenly distributed over the tremor cycle, peaking at a mean phase value of 177° (arrow) and in an opposite direction to the movement direction of tremor (lower trace).

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