Essential tremors and TMS study

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Abstract

Background: essential tremor (ET) is thought to emerge from activity in a distributed cerebello-thalamo-cortical network. It has been proposed that the network goes into oscillation because of some disorder of GABAergic inhibitory transmission. *Objective:* To test this idea by probing GABAergic circuitry in motor cortex using transcranial magnetic stimulation (TMS). *Methods:* Motor cortex excitability was examined using TMS in 21 patients with essential tremor and in 20 control subjects. Resting and active motor threshold (RMT, AMT) and input–output curves examined corticospinal excitability. Contralateral silent period (cSP) at a different range of stimulation intensities, and the ipsilateral silent period (iSP) using a stimulus intensity of 150% RMT were used as measures of GABAergic function. *Results:* RMT and AMT were significantly lower in patients than controls and patients had a steeper I/O curve. However, there were no significant differences in either cSP at different

intensities nor in iSP. *Conclusion:* We found no evidence in favour of the GABA hypothesis in ET.

Introduction

Essential tremor (ET) is one of the most common neurological disorders and is the most common type of tremor (Louis & Ferreira, 2010).The 2018 Movement Disorders (MDS) consensus criteria define classic ET as an isolated tremor syndrome of bilateral upper limb action tremor, with a duration>3 years, with or without tremor on other locations (e.g. head, voice, lower limbs), and without other neurological signs (e.g. dystonia, ataxia, and parkinsonism) (Bhatia et al 2018). Moderate and advanced stages of ET can be physically and socially disabling (Louis, 2005). The few medications that have been used to treat ET have demonstrated only modest efficacy (Deuschl, Raethjen, Hellriegel, & Elble, 2011).

The etiology and pathophysiology of ET are not yet well understood. In a recent review, Helmich et al postulate that it is a disorder of a cerebello-thalamo-cortical circuit. But what makes this circuit oscillate is still unclear. There are two main theories: the GABA hypothesis and the cerebellar degeneration hypothesis [10]. The former is supported by nuclear imaging that has shown abnormal 11C-flumazenil binding to GABA-A receptors in the ventrolateral thalamus, cerebellar dentate nucleus, and premotor cortex [14]. Furthermore, a postmortem study found reduced levels of GABA-A (35% reduction) and GABA-B (22e31% reduction) receptors in the dentate nucleus of patients with ET [15]. Markers of GABA-ergic dysfunction have also been reported in the locus coeruleus and pons, but these findings are less established [10]. Mally et al (REF) also found reduced levels of GABA in CSF of ET patients in one of the first early studies (Mally, Baranyi, & Vizi, 1996). It has been suggested that reduced GABAergic inhibition of dentate nucleus from Purkinje cells of the cerebellum might destablise the cerebello-thalmoo-cortical network and result in oscillatory activity and tremor [15].

Evidence of cerebellar degeneration has been described by Louis and colleagues, who observed structural changes in Purkinje cells and neighboring neurons, reduced Purkinje cell linear density with “empty baskets”, and Purkinje cell heterotopias [16]. There were also changes in the distribution of climbing fiber-Purkinje cell synapses [17]. However, not all findings have been replicated by other groups, possibly because of differences in sampling protocols, staining and assessment methods, and subject/ control definitions [1]. As with the GABA hypothesis, cerebellar Purkinje cell dysfunction may lead to cerebello-thalamo-cortical network dysfunction.

The purpose of the present study was to look for evidence of abnormal GABA function using TMS methods. Previous studies have failed to show any changes in

short interval intracortical inhibition (SICI), which is thought to test a GABAa interaction in motor cortex (Romeo et al 1998). However three studies show non-significant increases in the duration of the contralateral silent period, which is thought to depend on a GABAb pathway (Romeo et al 1998 and Shukla G et al 2003; Chuang et al, 2014). The silent period duration depends on stimulus intensity and in the previous studies only a single intensity was used. In addition the intensity is usually expressed relative to threshold, which assumes that the I/O curve is the same in ET as normal. Here we investigated the I/O curve and the recruitment of the silent period in 21 patients with essential tremors compared with age and sex matched healthy volunteers. We also examined the ipsilateral silent period, which is a transcallosally mediated inhibition of the non-stimulated cortex, and which is also thought to involve a GABAergic pathway.

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2. Methods

2.1 Patients

Twenty one patients were recruited from the outpatient clinic of Aswan University Hospital (14 males and 7 females, mean age 28.6±10.4 years; range, 15-56 years) during the period from Jan 2016-Jan 2017. A new consensus statement on the classification of tremors from the Task Force on Tremor of the International Parkinson and Movement Disorder Society (Bhatia et al., in press). According to this

consensus statement, tremor is defined along two main axes: clinical features (Axis 1) and etiology (Axis 2). The ET syndrome (on Axis 1) is defined as an isolated tremor syndrome of bilateral upper limb action tremor, with a duration>3 years, with or without tremor on other locations (e.g. head, voice, lower limbs), and without other neurological signs (e.g. dystonia, ataxia, and parkinsonism). The Task Force also defined an “ET plus syndrome”, where patients have an ET syndrome with additional “soft” neurological and systemic symptoms. Exclusion criteria for both ET syndromes are isolated focal tremors (voice, head), orthostatic tremor with a frequency >12 Hz, task- and position-specific tremors, and sudden onset and stepwise deterioration. (Deuschl, Bain, & Brin, 1998). Recent exposures to tremorogenic drugs or the presence of a drug withdrawal state or historical or clinical evidence of psychogenic tremor were also excluded.

Standard electrolyte panel, thyroid function tests, blood urea nitrogen and creatinin levels, liver function tests were done for each patients to exclude other causes of tremors. Scanning (CT) and or magnetic resonance imaging (MRI) was done if needed to exclude lesion.

The duration of ET ranged from 3 to 22 years: 14 patients had hand tremors, 2 patients had hand and foot tremors, 2 patients had hand, head and jaw tremor, 1 patient had hand and head tremor, 1 patient had hand, jaw and foot tremor, 1 patient had hand, head, jaw and foot tremor.

All cases were diagnosed by neurologists. 9 patients were already on treatment (9 of them on propranolol) with no satisfactory results and the other 12 were taking no treatment. Nine patients had a positive family history of ET. Out of the 21 patients ,1 had benign prostatic hyperplasia (Table 1).

Twenty one age-matched healthy volunteers (13 males and 8 females; mean age, 32.3±11.3 years; range, 17-55 years) represented the control population for assessment of cortical excitability. Patients and controls were asked not to take drugs that affect motor cortex excitability (dopaminergic drugs, tranquillizer or antiepileptic, antidepressant "SSRI") for at least one week before the study.
The study was approved by the Institutional Ethical Committee of Aswan University Hospital, and subjects gave their informed consent according to the declaration of Helsinki.

2.2 Experimental Setup and Design

Subjects sat in a comfortable chair. Electromyographic (EMG) recordings (Nihon Kohden 9400, Japan) from the abductor digiti minimi muscle of
right hand was acquired with silver–silver chloride surface electrodes, using a muscle belly–tendon set-up, with a 3-cm-diameter ground electrode placed on the wrist. The EMG parameters included a bandpass of 20 to 1000 Hz and a recording time window of 200 ms. The TMS was performed with a 90-mm figure-of eight coil connected to Magstim (UK) super rapid magnetic stimulator. Motor thresholds (MT) were determined after localization of the motor “hot spot” for the abductor digiti minimi muscle in left hemisphere as described in previous reports (Khedr, Ahmed, Ali, Badry, & Rothwell, 2015) (Elbeh et al., 2016). EMG signals were monitored and recorded for 20 ms before stimulation. Both RMT and AMT were expressed as a percentage of the maximal stimulator output (equal to 100%).

2.3 Input–output curve was evaluated at rest by increasing the intensity of stimulation in steps of 10% from 110% to 150% of RMT. Any trials in which there was detectable pre-stimulus EMG activity were discarded from the analysis on the

basis that this indicated that the participants were not completely relaxed. (Khedr et al 2018a, b)

2.4 The contralateral cortical silent period (cSP) of left hemisphere was evoked with stimuli of different intensities 110, 120, 130, 140, and 150% of RMT during isometric 50% maximum voluntary contraction of the contralateral abductor digiti minimi muscle. (Khedr et al 2018a,b)

2.5 Ipsilateral silent period (iSP) was assessed as previously described in Khedr et al 2018a, b.

2.6 Statistical Analysis

One- or two-way analysis of variance (SPSS version 16) was used to compare measures between patients and controls. Means ± standard deviation (SD) were used to represent data. The level of significance was set at $P<0.05$. A two factor repeated measures analysis of variance (ANOVA) with “groups” (patients versus control) and “intensity” as main factors was conducted for the I/O and cSP curves. When necessary, a Greenhouse–Geisser correction was applied to correct for non-sphericity. Post hoc unpaired t tests were carried out for specific comparisons of data from the two groups.

3 Results

3.1 Motor Thresholds

Both RMT (36.4±5.8) and AMT (30.1±5.8) for patients with ET were significantly lower than for control (41.5±6.8 and 33.9±6.9 respectively: intergroup comparison, $P = 0.01$ and 0.04 for RMT and AMT respectively).

3.2 Input–Output (I/O) Curve

A two-way repeated measures analysis of variance with main factors of “TMS intensity” (110, 120, 130,140, and 150% of RMT) and “group” (patients and controls) showed a significant " intensity X group interaction (F= 3.8 and P= 0.042) that was caused by a steeper input–output (I/O) relationship in the patients compared with controls. This was attributable to significantly higher amplitudes of MEP at 140, and 150% of RMT (unpaired t-test P = 0.014 and 0.039 uncorrected values respectively).

3.3 Duration of Contralateral Silent Period (cSP) at different TMS intensities

A two-way repeated measures analysis of variance with main factors of “TMS intensity” (110, 120, 130,140, and 150% of RMT) and “group” (patients and controls) showed no significant group X intensity interaction (F= 0.19 and P= 0.88) and no significant differences at any stimulus intensity.

3.4 Ipsilateral silent period (iSP)

The iSP was not significantly different between the patient group (29.1±9.6) and the controls (26.25 ± 8.2; p = 0.32).

Discussion

The present experiments were designed to examine in detail whether patients with ET have an abnormalities in two measures of cortical GABA function: contralateral and ipsilateral cortical silent period. In confirmation of two previous studies that found small but non-significant increases in CSP, the present data also show that there are no differences to normal over a range of stimulus intensities. There was also no difference in the duration of the ipsilateral silent period, thought to be due to a transcallosal GABAergic connection. The results therefore fail to support the GABA

hypothesis for ET. However, we did note that our patients had lower AMT and RMT compared with the control group as well as an increased I/O slope, which suggests that they had increased corticospinal excitability.

One previous study found no difference in short interval intracortical inhibition using paired pulse TMS (Romeo et al). This is thought to be due to activity in a GABA-a cortical pathway. However two studies did note small, but not significant increases in cSP duration in patients with ET (Shukla; Romeo). In those studies, the authors evoked the cSP at only one intensity which was expressed relative to the patients' resting motor threshold. Since the duration of the cSP increases with stimulus intensity we explored a larger range of intensities to test if more subtle deficits could be observed. However, there was no difference in cSP duration between the groups at any intensity.

The ipsilateral silent period has not been previously studied in ET, but is thought to be another measure that is influenced by GABA activity. We found the iSP duration to be the same in both groups, adding to the evidence that GABA function in motor cortex may be normal in ET.

Several other arguments have failed to find evidence in favour of GABA hypothesis in ET. Deng et al investigated the association between the GABAA receptor alpha-1 and ET in 76 familial ET patients. The association proved to be non-significant. The authors concluded that missense, nonsense, or splice site mutations in the coding regions of the GABAA1 gene are not a major genetic cause of ET (Deng, Xie, Le, Huang, & Jankovic, 2006). Another larger study included 503 ET patients and 818 controls investigated an association between polymorphisms in 15 GABAA and four GABA transporter genes in ET, the authors did not find any evidence of an association between GABAA and GABA transporter genes in ET (Thier et al., 2011).

The inability of several drugs targeting GABA system to control ET recorded various clinical trials also tends to suggest GABA function may not be the primary deficit in ET. These drugs include gabapentin, topiramate, tiagabine, and pregabaline (Connor, 2002; Ferrara et al., 2009; Gironell et al., 1999; Gironell, Martinez-Corral, Pagonabarraga, & Kulisevsky, 2008; Koller, Rubino, & Gupta, 1987; Zesiewicz et al., 2013).

No previous studies of ET have reported differences in motor thresholds (LO et al; Romeo et al; Shukla et al) and none have examined the I/O characteristics. It is possible that RMT and I/O curves could be influenced by “subthreshold” tremor activity in the sampled muscle, meaning that although notionally at rest and with EMG silence, the motoneurones were closer to threshold than the relaxed control volunteers and hence more readily excited by descending activity. It is difficult to discount this. However, the fact that that AMT, which cannot be influenced by “subthreshold” activity, also appeared to be slightly lower in patients suggests that further study of cortical excitability would be useful to explore in future studies.

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Results:

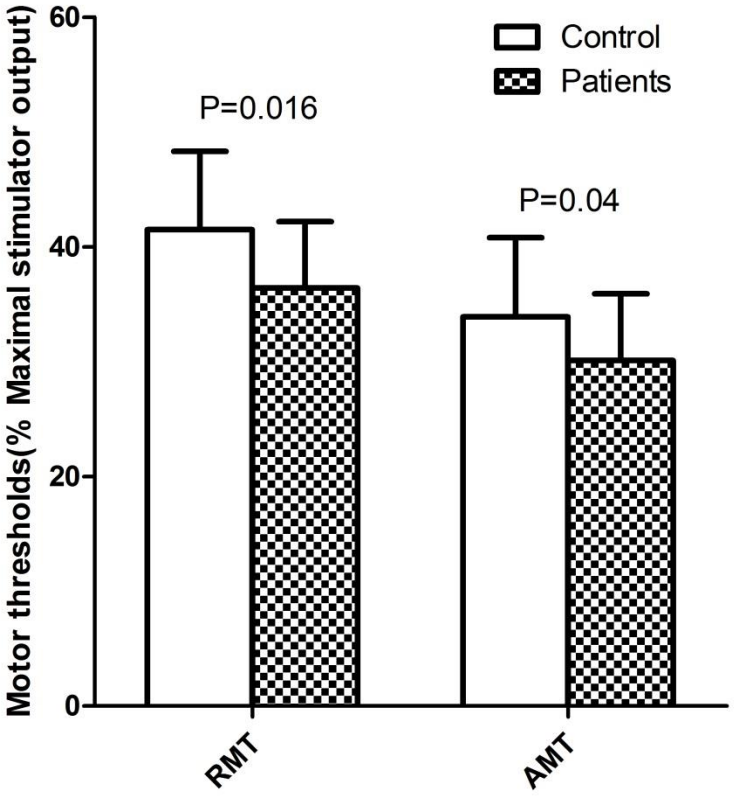
Table 1: Demographic and clinical data of studied patients with essential tremors

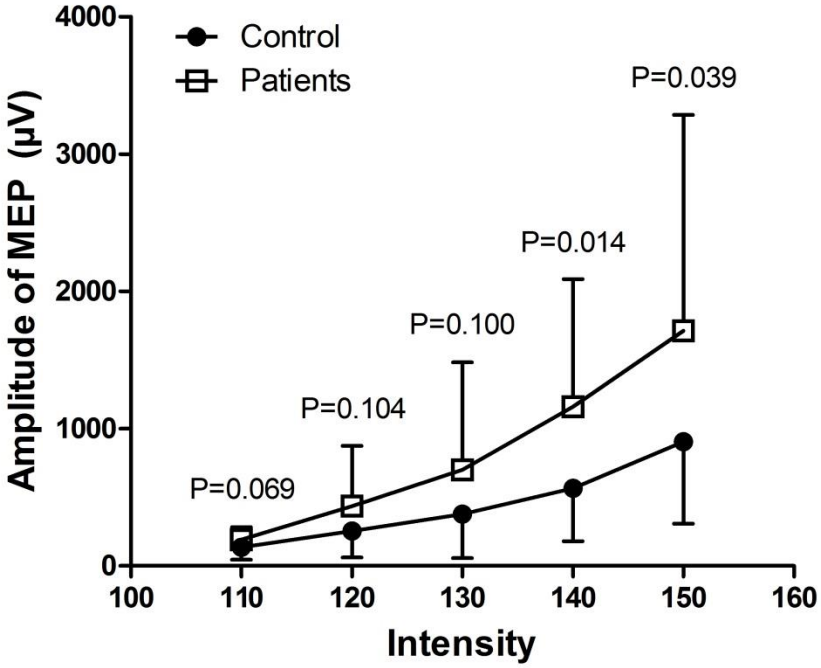
	Essential tremors	Control	P value
Sex Male/females	14 / 7 (66.6/33.3%)	13 / 8 (61.9/38.1%)	
Mean of age	28.6±10.4	32.3±11.3	0.35
Classification of tremors according to TRIG criteria number (%)	14 Definite ET (66.6%) 7 Probable ET (33.3%)		
Duration of ET diagnosis Mean ± SD (year) Range	 7.7 ± 5.3 3 year -22years		
Tremors localization Number (%)	Hands…. 14 (66.6%) Hands and feet…2 () Hands and head..1 () Hands, head and jaw….2 () Hands, jaw and feet….1 ()		

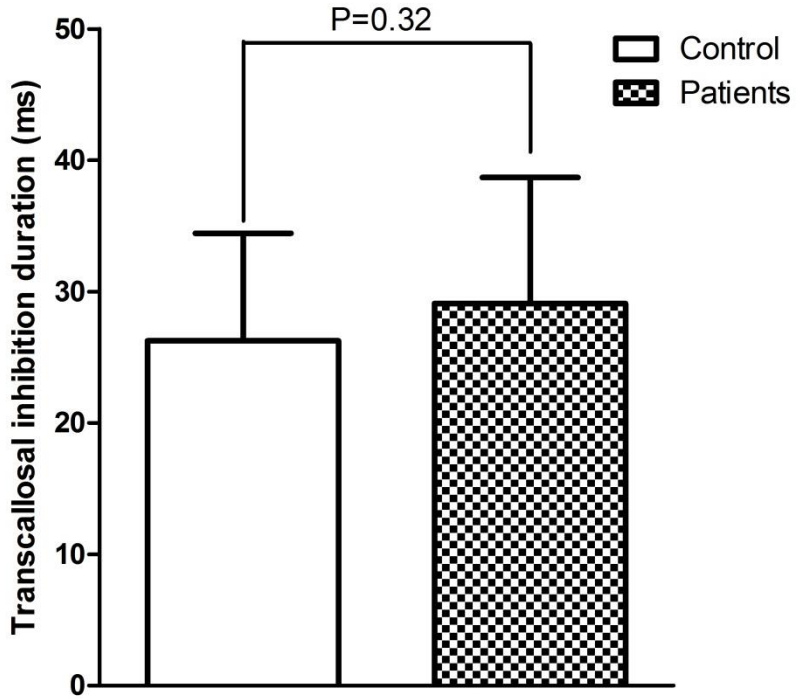
	Hands, head, jaw and the feet 1 ()		
Number of patients who received propranolol	11(52.4%)		
Positive family history of tremors	9 (47.3%)		

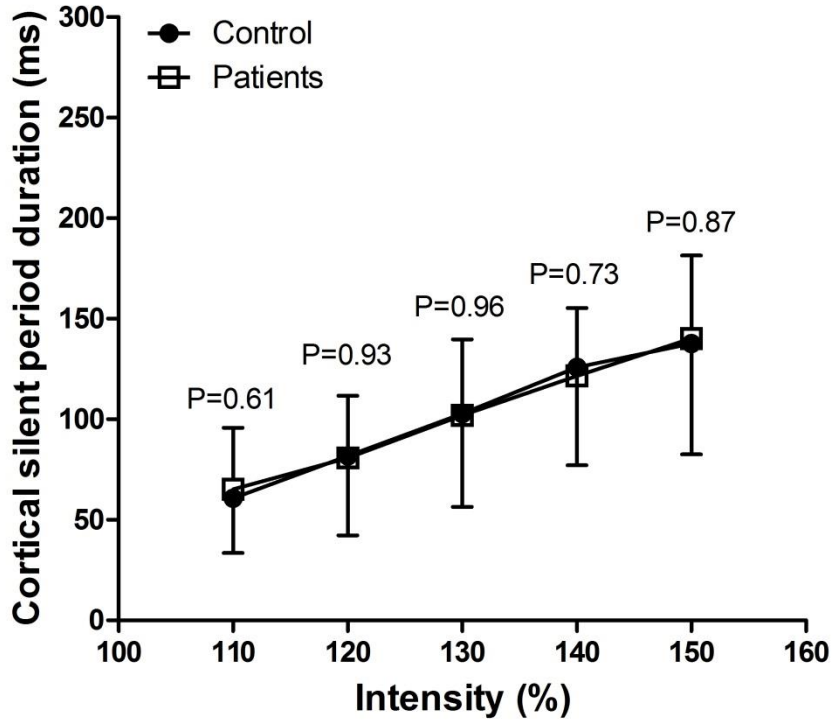
Table(2): Cortical excitability parameters of Essential tremors patients versus control group

	Patients N= 21 Mean ±SD	Control N=21 Mean ±SD	P value	Time x groups
Resting motor threshold (RMT)	36.4±5.8	41.5±6.8	0.016	
Motor active threshold(AMT)	30.1±5.8	33.9±6.9	0.04	
Amplitude of MEP in output curve(µv)				F= 3.8, df
110%	190.7 ± 92.5	136.3 ± 91.7	0.069	= 1.4, and
120%	435.5±439.2	254.1±191.9	0.104	P= 0.042
130%	700.5±782.7	377.5 ± 321.1	0.100	
140%	1159.2 ± 929.8	565.3 ± 385.4	0.014	
150%	1713.4±1573.3	905.2±597.1	0.039	
Cortical silent period duration in output curve (ms)				F= 0.19,
110%	65.2±30.6	60.8±27.3	0.610	df = 2.7,
120%	80.79±30.9	81.8±39.5	0.927	and P=
130%	102.0± 37.8	102.8±46.4	0.955	0.88
140%	121.6±33.8	125.8±48.6	0.725	
150%	140.2±41.3	137.6±55.1	0.870	
Transcallosal inhibition duration(ms)	29.1±9.6	26.25±8.2	0.32	


Motor thresholds(% Maximal stimulator output)
60
40
20
0
Control
Patients
P=0.016
P=0.04
RMT
AMT


Amplitude of MEP (μV)
4000
3000
2000
1000
0
Control
Patients
P=0.039
P=0.014
P=0.100
P=0.104
P=0.069
100
110
120
130
140
150
160
Intensity


P=0.32
Control
Patients
Transcallosal inhibition duration (ms)
50
40
30
20
10
0


Control
Patients
Cortical silent period duration (ms)
300
250
200
150
100
50
0
P=0.61
P=0.93
P=0.96
P=0.73
P=0.87
100
110
120
130
140
150
160
Intensity (%)