Experimental Neurology 297 (2017) 50–61

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Research Paper

# The differentiated networks related to essential tremor onset and its amplitude modulation after alcohol intake

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ARTICLE INFO

*Keywords:*
Essential tremor
Beamformer
DICS
MRI

ABSTRACT

The dysregulation of endogenous rhythms within brain networks have been implicated in a broad range of motor and non-motor pathologies. Essential tremor (ET), classically the purview of a single aberrant pacemaker, has recently become associated with network-level dysfunction across multiple brain regions. Specifically, it has been suggested that motor cortex constitutes an important node in a tremor-generating network involving the cerebellum. Yet the mechanisms by which these regions relate to tremor remain a matter of considerable debate. We sought to discriminate the contributions of cerebral and cerebellar dysregulation by combining high-density electroencephalography with subject-specific structural MRI. For that, we contrasted ET with voluntary (mimicked) tremor before and after ingestion of alcohol to regulate the tremorgenic networks. Our results demonstrate distinct loci of cortical tremor coherence, most pronounced over the sensorimotor cortices in healthy controls, but more frontal motor areas in ET-patients consistent with a heightened involvement of the supplementary motor area. We further demonstrate that the reduction in tremor amplitude associated with alcohol intake is reflected in altered cerebellar – but not cerebral – coupling with movement. Taken together, these findings implicate tremor emergence as principally associated with increases in activity within frontal motor regions, whereas modulation of the amplitude of established tremor relates to changes in cerebellar activity. These findings progress a mechanistic understanding of ET and implicate network-level vulnerabilities in the rhythmic nature of communication throughout the brain.

## 1. Introduction

Tremor manifests as a common symptom in a diverse range of movement disorders and can be a devastating burden on everyday life. Essential tremor (ET) is the most commonly encountered entity, in which patients develop postural and/or intentional tremor predominantly of the upper extremities, although other parts of the body may also be affected. Despite the high prevalence of ET its pathomechanisms remain largely unknown.

Like many tremor syndromes, early studies posited a single oscillator hypothesis – that one brain region accounts for tremulous outflow. This notion has been displaced in favour of disruption in a more widespread 'tremor network' comprising multiple brain regions (for a review see Raethjen and Deuschl, 2012). In this context, hypersynchronisation of the cerebello-thalamocortical pathways has become a prime focus of research for several reasons. Firstly, abundant behavioural and imaging studies implicate cerebellar disturbances in ET (Bhalsing et al., 2013; Jenkins et al., 1993; Popa et al., 2013; Wills et al., 1994). Secondly, tremor relief by medication (Boecker et al., 2010) – or reduction in tremor after alcohol intake – closely relate to changes in cerebellar activation (Boecker et al., 1996). Finally, medically refractory tremor may be treated by inducing functional or

*Abbreviations:* BEM, boundary element method; CI, confidence interval; CSD, cross-spectral density; DBS, Deep Brain Stimulation; DICS, Dynamic Imaging of Coherent Sources; DPSS, discrete prolate spheroidal sequences; EDC, *Musculus extensor digitorum communis*; EMG, Electromyography; ET, essential tremor; FoV, field of view; M1, primary motor cortex; MDEFT 3D, Modified driven equilibrium Fourier Transform in 3D; MEG, Magnetoencephalography; PCA, principle component analysis; RMS, root mean square; ROI, region of interest; SMA, supplementary motor area; TE, Echo time; TI, Inversion time; TR, Repetition time; VLp, posterior part of the ventrolateral thalamus

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http://dx.doi.org/10.1016/j.expneurol.2017.07.013
Received 15 May 2017; Received in revised form 29 June 2017; Accepted 24 July 2017
Available online 25 July 2017
0014-4886/ 

structural thalamic lesions, most likely targeting abundant cerebellar input to and dense cortical projections from the posterior parts of the ventrolateral thalamus (VLp, Kelly and Strick, 2003; Middleton and Strick, 2001).

Intraoperative recordings during Deep Brain Stimulation (DBS) electrode implantation within the VLp, or electrophysiological studies during the days thereafter have begun to shed light on the underlying pathophysiology of ET, yet are at the same time hampered by our lack of knowledge about the functional organization of thalamocortical pathways underlying normal motor function. Thus, it has been demonstrated that oscillatory tremor activity has a topographic representation in the VLp (Pedrosa et al., 2012), that relies heavily on sensory feedback (Pedrosa et al., 2014; Schnitzler et al., 2009). Moreover, electrical pulses delivered to the VLp may disrupt tremor when delivered both at high frequencies (Benabid et al., 1991) and at lower frequencies when locked to certain phases of tremor oscillations (Cagnan et al., 2013, Cagnan et al., 2016). The most effective thalamic targets for interventions remain the cerebellar-recipient zones, emphasising the critical nature of this node.

More recently, however, considerable literature has developed around cerebral involvement in ET. Specifically, cortical motor areas appear to be involved in the tremulous drive to muscles (Govindan et al., 2006; Hellwig et al., 2001). In addition, magnetoencephalographic (MEG) results and studies applying combined EEG and local-field potential recordings revealed tremor-related synchronisation between cortical motor areas, the thalamus and the cerebellum (Marsden et al., 2000; Muthuraman et al., 2012; Schnitzler et al., 2009). Current theories on ET pathomechanisms implicate both cerebellar and cerebral motor regions (Buijink et al., 2015; Neely et al., 2015). Specifically, there is an emerging notion that dysregulation in cerebellar outflow to cerebral cortex results in compensation by SMA that mitigates tremulous activity (Gallea et al., 2015). When actively engaged, such as during motor tasks, the compensatory role of the SMA breaks down leading to peripheral tremor.

The above observations suggest at least two key nodes of interest in the generation and modulation of essential tremor; the cerebellum and the SMA. Tremor-related SMA activity has been hypothesised to be primarily compensatory. As such it should be absent when healthy subjects voluntarily mimic tremor. In contrast, the response of VLp interventions suggests that the cerebellum and its outflow may be involved in more directly promoting tremor. As such, we predict a relationship between tremor-related cerebellar activity and manipulations of tremor amplitude. To test these predictions we studied the functional connectivity of cerebral and cerebellar regions with tremor output using high-density EEG (HD-EEG) in cohorts of ET-patients and age- and gender-matched healthy control subjects and manipulated tremor amplitude through alcohol intake.

## 2. Methods

The study was approved by the local Ethics committee and carried out in accordance with the Declaration of Helsinki. All patients had given their written informed consent prior to participating.

### 2.1. Patients and clinical evaluation

For this pre-post study, 20 right-handed patients suffering from ET according to the diagnostic criteria of the Consensus statement of the Movement Disorder Society Group (Deuschl et al., 1998) were investigated. Three ET-patients were characterised as mixed-handed by the Edinburgh handedness inventory (EHI scores $< 50$) and were replaced by three further right-handed ET-patients. Twenty right-handed, gender- and age-matched healthy volunteers served as control group. To rule out a significant level of cognitive impairment, participants underwent a dementia screening test (DemTect) with cut-off below 12 (Kalbe et al., 2004). Response times were evaluated in a simple task in which subjects were instructed to press a button following a visual cue.

No control subject was under medication potentially influencing the central nervous system, but two ET-patients took primidone and two more received propranolol. These patients were asked to discontinue their medication at least 24 h in advance of the study. All other patients were untreated. For more details on ET-patients, cf. Supplementary data.

### 2.2. Electrophysiological recordings

Participants were seated in a reclining armchair with neck and back supported and EEGs were recorded using an elastic cap with 128 electrodes mounted in a spherical array (Easy-Cap GmbH, Herrsching, Germany). To maintain electrode impedances below 10 kΩ, conduction gel was applied. The used caps were standardized and placed according to the 10/10 system. Individual electrode locations thus resulted from interpolation from the individual 3T MRI scans and given fiducial points (see below). The relationship between electrodes and MRI was inspected visually for every subject. Additionally, activity of the *Musculus extensor digitorum communis* (EDC) of the right forearm was recorded using surface electromyography (EMG) electrodes while a tri-axial accelerometer placed on the centre of the right wrist registered tremulous arm activity. All data were recorded on a BrainAmp® standard amplifier (Brain Products GmbH, Gilching, Germany), low-pass filtered at 1 kHz and digitized at a sampling rate of 5 kHz. The EMG of the EDC of an ET-patient is illustrated in Fig. 2.

### 2.3. Motor paradigm

The motor paradigm consisted of two conditions: i) a resting state (baseline) in which participants were asked to remain in a relaxed position with their arm supported and ii) voluntary elevation of the right forearm by about 10–15 cm above the arm of an armchair with an extended wrist and extended fingers for 3.5 s while their elbow remained on the arm of the chair. These short periods of postural contraction were selected to focus on neurophysiological changes underpinning the onset of sustained tremor and to avoid fatigue which may have occurred during longer trials. Our task elicited involuntary tremor in ET-patients, whereas control subjects were instructed via video to perform rhythmic movements of the forearm and wrist to mimic tremor. Both tasks were thoroughly explained in advance of the experiments and all participants received the opportunity to practise them. The sequence of conditions was randomised with an unequal allocation ratio of 2:1 (tremor vs. rest conditions). Participants were instructed to fixate the centre of a computer screen during the experiment and to avoid excessive swallowing or blinking during the tasks. Every trial consisted of a task instruction displayed for 5 s, followed by a red fixation cross (foreperiod; randomised duration between 1.3 and 4.8 s), then a green cross for the duration of the trial (3.5 s). At the end of the trial the red cross reappeared for 2.5 s (see Fig. 1). Each task was repeated 18 (rest condition) and 36 times (tremor).

To analyse modulation of tremor, after the completion of the first experiment all participants were asked to consume 1.5 alcohol units (one bottle of 330 ml, 4.8 vol% “Kölsch”, i.e. local lager beer) and the experiment was repeated 30 min after alcohol intake.

### 2.4. Magnetic resonance imaging data acquisition and image pre-processing

Structural MR images were acquired using a 3T Siemens Trio Scanner (Siemens Healthcare, Erlangen, Germany). A structural data set was recorded with a twelve channel array head coil using a whole brain field of view (FoV) and with the following configuration: MDEFT-3D (T1-weighted, TR = 1930 ms, TI = 650 ms, TE = 5.8 ms, image dimension = 256 × 256 × 128, sagittal slices with a resolution of $1 \times 1 \times 1.25\ mm^3$, flip angle 18°). One ET-patient declined to undergo an MRI scan citing claustrophobia.