Motor network disruption in essential tremor: a functional and effective connectivity study

Arthur W. G. Buijink, A. M. Madelein van der Stouwe, Marja Broersma, Sarvi Sharifi, Paul F. C. Groot, Johannes D. Speelman, Natasha M. Maurits and Anne-Fleur van Rootselaar

Although involvement of the cerebello-thalamo-cortical network has often been suggested in essential tremor, the source of oscillatory activity remains largely unknown. To elucidate mechanisms of tremor generation, it is of crucial importance to study the dynamics within the cerebello-thalamo-cortical network. Using a combination of electromyography and functional magnetic resonance imaging, it is possible to record the peripheral manifestation of tremor simultaneously with brain activity related to tremor generation. Our first aim was to study the intrinsic activity of regions within the cerebello-thalamo-cortical network using dynamic causal modelling to estimate effective connectivity driven by the concurrently recorded tremor signal. Our second aim was to objectify how the functional integrity of the cerebello-thalamo-cortical network is affected in essential tremor. We investigated the functional connectivity between cerebellar and cortical motor regions showing activations during a motor task. Twenty-two essential tremor patients and 22 healthy controls were analysed. For the effective connectivity analysis, a network of tremor-signal related regions was constructed, consisting of the left primary motor cortex, premotor cortex, supplementary motor area, left thalamus, and right cerebellar motor regions lobule V and lobule VIII. A measure of variation in tremor severity over time, derived from the electromyogram, was included as modulatory input on intrinsic connections and on the extrinsic cerebello-thalamic connections, giving a total of 128 models. Bayesian model selection and random effects Bayesian model averaging were used. Separate seed-based functional connectivity analyses for the left primary motor cortex, left supplementary motor area and right cerebellar lobules IV, V, VI and VIII were performed. We report two novel findings that support an important role for the cerebellar system in the pathophysiology of essential tremor. First, in the effective connectivity analysis, tremor variation during the motor task has an excitatory effect on both the extrinsic connection from cerebellar lobule V to the thalamus, and the intrinsic activity of cerebellar lobule V and thalamus. Second, the functional integrity of the motor network is affected in essential tremor, with a decrease in functional connectivity between cortical and cerebellar motor regions. This decrease in functional connectivity, related to the motor task, correlates with an increase in clinical tremor severity. Interestingly, increased functional connectivity between right cerebellar lobules I–IV and the left thalamus correlates with an increase in clinical tremor severity. In conclusion, our findings suggest that cerebello-dentato-thalamic activity and cerebello-cortical connectivity is disturbed in essential tremor, supporting previous evidence of functional cerebellar changes in essential tremor.
Introduction

Essential tremor is one of the most common neurological disorders, and is characterized by a progressive postural and kinetic tremor (Louis and Ferreira, 2010). Evidence of alleviation of tremor following thalamic deep brain stimulation, and after stroke anywhere in the cerebello-thalamo-cortical network, prompted the hypothesis of essential tremor as an ‘oscillating network’ disorder (Dupuis et al., 2010; Raethjen and Deuschl, 2012). Evidence is accumulating that the cerebellum plays an important role in the pathophysiology of essential tremor (Passamonti et al., 2011; Grimaldi and Manto, 2013; Buijink et al., 2015). An important supporting feature is the positive effect of alcohol on essential tremor (Haubenberger et al., 2013). Furthermore, emerging clinical features such as ataxic gait (Stolze et al., 2001; Fasano et al., 2010; Hoskovcová et al., 2013), eye movement abnormalities (Helmchen et al., 2003; Kronenbuerger et al., 2007; Gitchel et al., 2013) and intention tremor (Deuschl et al., 2000; Louis et al., 2009) all point to cerebellar changes in essential tremor. Whether these abnormalities relate to structural or functional cerebellar changes is under debate. Pathology studies show an incongruent picture, but provide evidence for neurodegeneration of the cerebellum (Louis, 2014). There is evidence for morphometric changes and possibly loss of Purkinje cells (Louis et al., 2007; Rajput et al., 2012; Babij et al., 2013; Lin et al., 2014). Moreover, changes in the dentate nucleus have been established, with decreased numbers of GABA receptors reported in essential tremor cases (Paris-Robidas et al., 2011). On the other hand, imaging studies show a striking lack of convincing structural involvement, but do provide evidence for functional abnormalities of the cerebellum (see Sharifi et al., 2014 for a review).

Although the notional involvement of the cerebello-thalamo-cortical network, and of the cerebellum in particular, is becoming increasingly evident, the source of oscillatory activity in essential tremor remains largely unknown (Schnitzler et al., 2009; Muthuraman et al., 2012). To elucidate the mechanisms of tremor generation it is of crucial importance to study network dynamics within the cerebello-thalamo-cortical network. Using a combination of EMG and functional MRI (EMG-fMRI), we can record the peripheral manifestation of tremor simultaneously with brain activity related to tremor generation. Previous studies by our group and others have proven that EMG-fMRI allows identification of brain areas involved in the generation of tremor (van Rootselaar et al., 2007, 2008; Helmich et al., 2011; Contarino et al., 2012). In a recent EMG-fMRI study, we have demonstrated tremor-related increases in activations in specific somatomotor regions of the bilateral cerebellum in essential tremor (Broersma et al., unpublished results). In the current, complementary study, we investigate effective and functional connectivity within the tremor network, incorporating information from the concurrently recorded EMG signals to provide better insight into changes within the cerebello-thalamo-cortical network in essential tremor. While functional connectivity describes simple correlations between spatially segregated neuronal events, effective connectivity tries to estimate the underlying, direct, causal connections, which is of crucial importance in the investigation of the underlying biological network (Friston, 1994).

Our first aim was to study intrinsic activity of regions within the cerebello-thalamo-cortical network by using an effective connectivity analysis called dynamic causal modeling (DCM). DCM explores how observed brain activations are generated by estimating the effective connectivity between and within specified regions of interest (Friston et al., 2003). For instance, DCM has been shown to be able to identify the correct neural driver behind epileptic seizures by including the occurrence of spike-and-wave discharges obtained from concurrently recorded EEG signals into the model (David et al., 2008). We hypothesize that internal cerebellar feedback is altered in essential tremor. The cerebellum is thought to have multiple somatotopic representations (Buckner et al., 2011). However, until now these have not been studied nor discussed separately in essential tremor. Hence, we will look specifically at intrinsic feedback changes within the anterior motor regions, composed of cerebellar lobules I to V, and posterior motor regions, mainly composed of cerebellar lobule VIII, of the cerebellum (Buckner et al., 2011).

Our second aim was to objectify how the functional integrity of the cerebello-thalamo-cortical network is affected by any cerebellar changes in essential tremor, by means of a functional connectivity analysis, investigating the functional connections between cerebellar and cortical motor regions using a seed-based correlation approach (Buckner et al., 2011; Helmich et al., 2011). As suggested in a previous study, due to altered cerebellar functioning, we expected to find consequential alterations to functional connectivity between cerebellar and cortical motor regions in essential tremor (Neely et al., 2014).
Advancing insights strongly suggest that patients with essential tremor form a widely heterogeneous group, possibly giving rise to conflicting results between essential tremor studies (Louis, 2009). In this study, we have defined a homogeneous group of essential tremor patients, with a clear diagnosis according to the criteria defined by the Tremor Investigation Group (Bain et al., 2000) and a positive effect of propranolol, a drug with level A evidence for treatment of essential tremor (Deuschl et al., 2011).

Materials and methods

Participants

In total, 40 patients and 22 healthy controls were included. This study was conducted in two academic hospitals in The Netherlands: the Academic Medical Center in Amsterdam and the University Medical Center Groningen. Patients with a definite diagnosis of essential tremor according to criteria defined by the Tremor Investigation Group were selected if they fulfilled the following criteria (Bain et al., 2000): bilateral upper limb tremor, an age at onset < 65 years, and a disease duration > 5 years. Furthermore, patients had to be right handed and report a positive effect of propranolol on the tremor. Healthy controls, matched for age, gender and handedness, were selected. Exclusion criteria were: a score < 26 on the Mini-Mental State Examination, neurological disorders (for patients: other than essential tremor), age < 18 years, the use of medication affecting the CNS and magnetic resonance-related contra-indications. Tremor severity was assessed OFF medication by an experienced movement disorders neurologist (J.D.S.) using the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) parts A and B (Fahn, 1993). Medication was discontinued at least 3 days before the study. Item A on the TRS represents tremor severity of the arms in rest, posture and during action. Item B represents clinical assessment of tremor severity during tremor-inducing task performance. Finally, tremor severity was assessed using a Visual Analogue Scale (VAS). The study was approved by the local medical ethical committees and conducted according to the Declaration of Helsinki. All participants gave written informed consent.

Functional MRI task

A functional MRI scan was performed, while EMG was recorded simultaneously, OFF medication. Participants executed a motor task in which they were instructed to alternate 21 periods of 30 s rest with 20 periods of 30 s performing the task. Before scanning, subjects were first carefully instructed about the motor task and then practised it outside the scanner to ascertain correct task performance. Patients with essential tremor performed right hand and arm extension, the aim being to induce action tremor. Healthy controls were instructed to mimic a tremor during all task blocks by extending the right arm and performing self-paced wrist flexion-extension. As essential tremor is known to aggravate during mental tasks, an additional silent reading task was presented during half of all action blocks, with the aim to evoke more variation in tremor amplitude (Koller and Biary, 1989). During the other half of action blocks, a visual task instruction ‘stretch out your arm’ was presented during scanning, which elicited tremor as well. All instructions were presented using slides projected onto a screen located outside the scanner bore and visible by way of a mirror. Correct task performance was assessed by visual inspection during scanning.

Data acquisition and preprocessing

For full details of functional MRI and EMG acquisition and preprocessing see the online Supplementary material. Images were acquired using a Philips 3 T Magnetic Resonance scanner at both sites. T2*-weighted, 3D functional images were obtained using multislice echo planar imaging (EPI) with an echo time of 30 ms and a repetition time of 2000 ms. EMG was recorded simultaneously [BrainProducts (UMCG) and MicroMed (AMC)] from five right arm muscles. EMG data were corrected for magnetic resonance artefacts using the magnetic resonance artefact correction algorithms (Imaging Artefact Reduction method) (Allen et al., 2000; UMCG data) embedded in the BrainVision Analyzer software (BrainProducts) and FARM (functional MRI artefact reduction for motion) (van der Meer et al., 2010; AMC data). Functional MRI data were analysed using SPM12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm, v6225, DCM version 12), and included standard preprocessing (Supplementary material). Inspection of the EMG was used to correct the block design regressor for actual onsets and offsets of the motor task. For each subject, scan-by-scan EMG power was calculated in a 5-Hz band around the peak tremor frequency. Finally, this EMG ‘tremor’ vector was orthogonalized with respect to the block regressor, scaled to the maximum value per subject to ensure that the variance was similar between subjects, convolved with the canonical haemodynamic response function and used as a regressor (residual-EMG) in the General Linear Model (van Rootselaar et al., 2007). As motion-related and other non-neuronal signal changes are effectively reduced by global signal regression, tissue-based signals and their first derivative were also used as nuisance regressors and were calculated as the average signal across all voxels within the whole-brain mask (Power et al., 2014). Each single-subject first-level model thus consisted of two block regressors for the motor task, a residual-EMG regressor, six movement regressors and two global signal regressors. For the functional connectivity analysis, the residual-EMG regressor was excluded from the first-level models as the objective of this analysis was to primarily look at the integrity of the motor network without concurrently assessing tremor severity. Brain activations during motor task execution and tremor-related (EMG-based) activations are reported elsewhere in more detail (Broersma et al., unpublished observations). In short, motor task-related activations were found in the well-known upper-limb motor network, i.e. both for patients with essential tremor and healthy controls in motor, premotor and supplementary motor areas. In patients with essential tremor, we found tremor-related (EMG-based) activations in the left primary motor cortex (M1), supplementary motor area (SMA), premotor cortex (PMC) and thalamus, and bilaterally in the cerebellum: in left lobules VI and V, and in right lobules V, VI, and VIII, and in the brainstem. Ipsilateral cerebellar activity was related to mimicked-tremor in healthy participants. Tremor-based
activations are used in the effective connectivity analysis; motor-task-based activations are used in the functional connectivity analysis. Finally, the amount of head movement during scanning was estimated by calculating the summed Euclidean distance between the first and last scan per individual subject for translation (i.e. x, y and z direction) and rotation (i.e. pitch, roll, yaw) separately, and compared between healthy patients and healthy controls using two-sample two-tailed t-tests (Helmich et al., 2011).

**Effective connectivity: Dynamic Causal Modelling**

DCM models how neural activity within a network of brain regions is driven by external perturbations that result from experimentally controlled manipulations (Friston et al., 2003). These perturbations are described by means of external inputs u that can enter the model in one of two ways (Friston et al., 2003). First, they can elicit responses through direct influences on specific regions and can be described as ‘driving’ inputs or ‘stimulus-bound perturbations’. An example would be the command to stretch out your arm. Second, they can change the strength of coupling among or within regions, and can be described as ‘modulatory’ inputs or ‘contextual perturbations’. For example, fluctuations in tremor severity over time could change the intrinsic activity within regions of the cerebello-thalamo-cortical network. An important concept in DCM is that regions contain self-inhibitory properties, mediated by self-connections (‘intrinsic’ or within-region connections), preventing runaway outbursts of neural activity. The left M1, left PMC, left SMA, left ventral lateral nucleus of the thalamus, right cerebellar lobule V/VI and right cerebellar lobule VIII were included in our models as these regions have been associated with tremor previously using functional MRI (Bucher et al., 1997; Neely et al., 2014) and showed tremor-related (EMG-based) activations in the patient group, as mentioned previously (Broersma et al., unpublished results). Regions were defined for each patient individually, based on activations associated with the residual-EMG regressor, and centred at the location of the local maxima with a 4 mm radius, within 10 mm of the group maximum (MNI coordinates: M1 x = -36 y = -22 z = 61; PMC x = -28 y = -22 z = 54; SMA x = -2 y = -14 z = 55; thalamus x = -12 y = -24 z = -1; cerebellar lobule V/VI x = 34 y = -50 z = -25; cerebellar lobule VIII x = 21 y = -52 z = -56). We assumed full endogenous connectivity between regions, with the exemption of connections between cerebellar regions and the thalamus (only unidirectional from cerebellum to thalamus) and between cortical and cerebellar regions (only unidirectional from cortical to cerebellar regions) based on neuronal tracing studies in macaque monkeys (Fig. 1) (Middleton and Strick, 2000), leaving 28 endogenous connections. We furthermore assumed a direct effect of the motor task on the activity of all premotor regions (left SMA, left PMC) (Goldman-Rakic et al., 1992; Wang et al., 2011). The task regressor was divided into two separate regressors to compare the direct effects of the motor task and the motor plus silent reading task to each other.

The residual EMG regressor, which represents variations in tremor amplitude over time, was included as a modulatory input on the intrinsic connections of all regions (Fig. 2A). In this manner, the residual EMG regressor functions as a modifier of the ‘state’ a region is in depending on the intensity of tremor. Since the dentate nucleus is an important region within the tremor network, but not included as a node in our network, additional interest was focused on the cerebello-thalamic connections. These connections represent the net effect of the cerebello-dentatal output onto the thalamus. Therefore, modulatory input of tremor onto the cerebello-thalamic connections was added to the model space (Fig. 1). This gave a total of 22 × 128 models. Figure 1 gives an overview of the DCM framework for this study; a list of models and their modulatory inputs is provided in the Supplementary material. Models were compared using Bayesian model selection (BMS) on group level (Penny et al., 2010; Stephan et al., 2010; Rigoux et al., 2013). Subsequently, a *post hoc* Bayesian model selection family analysis was used to evaluate the exceedance probabilities of a modulatory effect on each region or connection. The exceedance probability (D) corresponds to the belief that a model or family is more likely than any other, given the data from all subjects (Penny et al., 2010).

We then used random effects Bayesian model averaging (BMA) on the winning half of model space, in which parameter estimates are weighted by the model evidence to compare resulting coupling parameters (Stephan et al., 2010; Torrisi et al., 2013). This method is convenient when many models are compared and when there is no obvious winning model. The posterior densities of the parameters are calculated across subjects and across the winning half of models. More weight is given to the models with the highest posterior probability according to Bayes’ rule (Penny et al., 2010). The resulting coupling parameters represent connection strengths (Friston et al., 2003). The posterior distributions are calculated using a Gibbs sampling approach by drawing samples from a multinomial distribution of posterior beliefs for the included models (Penny et al., 2010). Subsequently, posterior means and standard deviations of parameters were obtained and tested for significance using one-sample two-tailed t-tests. Because we tested 40 parameters of interest (28 endogenous, eight modulatory and four task inputs) we have adjusted the significance threshold using the Bonferroni method \[ \alpha = 1 - (1 - \alpha)^{1/40} = 0.001282 \]. Positive coupling parameters suggest a facilitation of neural activity, whereas negative coupling parameters can be interpreted as inhibition of neural activity. Coupling parameters are reported in Hz, reflecting the amount of activity that ‘flows’ from one region to another per second. For the effective connectivity analysis, we chose to include only essential tremor patients and not to include a group comparison as the two ‘tasks’ performed by both groups (mimicking tremor versus real tremor) are qualitatively different.

**Functional connectivity: seed-based correlation analysis**

To assess the functional integrity of the motor network in essential tremor, we performed separate seed-based functional connectivity analyses between six areas showing the strongest response relating to the motor task in essential tremor patients and healthy controls: left M1, left SMA and right cerebellar hemisphere lobules IV, V, VI and VIII (Supplementary
material). We chose to look at activations related to the motor task because this allowed us to compare patients with essential tremor to healthy controls, and because functional coupling between cerebellar and cortical motor regions is most specific during motor tasks (Buckner et al., 2011). Time courses of all regions were obtained by extracting the first eigenvariates with SPM12, adjusted for effects of interest, for significant voxels using a threshold of $P < 0.001$ (uncorrected) (Friston et al., 2006; Buckner et al., 2011; Helmich et al., 2011). Regions were defined for each subject, individually centred at the location of the local maxima with a 4-mm radius, within 10 mm of the group maximum (MNI coordinates: M1 $x = -28$ $y = -28$ $z = 53$; SMA $x = -2$ $y = -8$ $z = 57$; cerebellar lobule I-IV $x = 4$ $y = -64$ $z = -21$; cerebellar lobule V $x = 14$ $y = -50$ $z = -19$; cerebellar lobule VI $x = 22$ $y = -50$ $z = -25$; cerebellar lobule VIII $x = 24$ $y = -58$ $z = -49$). For each subject and each region, we then entered this time course as a regressor in a multiple regression analysis together with the task regressor and nuisance regressors. The task regressor was added to exclude activations related to the motor task. For the second-level between group comparisons, non-parametric permutation tests were performed; this is preferred over parametric methods as this does not require that the data are normally distributed (Thirion et al., 2007) [Statistical non-Parametric Mapping 13b, http://www.sph.umich.edu/ni-stat/SnPM/ (Holmes et al., 1996) 10 000 permutations]. Contrasts were built to test (i) for significant between-group differences in functional connectivity; and (ii) for significant correlations of functional connectivity.
within the patient group with clinically assessed tremor severity (TRS A + B), subjectively assessed tremor severity (VAS) and disease duration. Correlations between objective (i.e. TRS A + B) and subjective (i.e. VAS) measures of tremor severity are known to be limited (van der Stouwe et al., 2015). We expect TRS A + B to give the best representation of tremor amplitude, whereas VAS scores entail several entities such as tremor severity, psychological and social factors (van der Stouwe et al., 2015). A cluster-wise inference was used \[ P < 0.05 \text{ (FWE corrected), cluster-forming threshold } P < 0.001 \]. To test specifically for changes in cerebellar-cortical correlations, seed-based correlations were masked with either the whole cerebellum (for the M1 and SMA seed) (Diedrichsen, 2006) or a cerebral motor mask including left M1, left PMC, left SMA and left thalamus (for the cerebellar seeds) (Eickhoff et al., 2005). The probabilistic atlas of the cerebellar cortex and the AAL toolbox were used to define anatomical locations of activations (Eickhoff et al., 2005; Diedrichsen et al., 2009).

**Results**

**Participants**

Eighteen patients and one healthy control were excluded for further analysis. Reasons for exclusion of data sets were sudden excessive head movements during scanning causing striping artefacts (one patient, one healthy control), insufficient tremor during functional MRI data collection (16 patients) or failure of equipment during scanning (one patient). Healthy controls (14 male) had a median age of 56.5 years (range 20–72). For the effective connectivity analysis, four additional patients were excluded because they did not show significant tremor-related activations at an uncorrected threshold of \[ P < 0.001 \], a prerequisite for the DCM analysis, thus 18 patients were included in the effective connectivity analysis. See Table 1.
for a full overview of included essential tremor patients. Included patients and healthy controls exhibited similar amounts of head movement during scanning [mean translation parameters: patients: 2.64 mm standard deviation (SD) 1.36; healthy controls: mean translation parameters 2.68 mm (SD 0.97), \( t(42) = 0.2720, P = 0.92 \); and mean rotation parameters: patients: 0.056\(^\circ\) (SD 0.03); healthy controls 0.052\(^\circ\) (SD 0.03), \( t(42) = 0.43, P = 0.67 \)].

### Effective connectivity: Bayesian Model Selection

**Table 1** Patients’ characteristics

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<th>Gender</th>
<th>Tremor frequency (Hz)</th>
<th>TRS A + B</th>
<th>Duration (years)</th>
<th>Family history</th>
<th>Propranolol use (mg)</th>
<th>VAS-score OFF medication</th>
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Excluded from the effective connectivity analysis:

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Median (range) 59.5 (21–80) M: 12 F: 10 7.5 (5–10) 11 (4–31) 30.5 (5–62) +: 19 –: 3 65 (20–320) 6.0 (2.6 – 9.2) +: 13 –: 2 7

Four patients were excluded for the effective connectivity analysis due to absent significant tremor-related activations at an uncorrected threshold of \( P < 0.001 \). VAS: range 0–10. TRS A + B scores were assessed while OFF medication. + = positive; – = negative; ? = unknown.

Effective connectivity: Bayesian Model Selection

Figure 2B gives an example of observed and predicted blood oxygen level-dependent time courses of one subject, based on the DCM estimation. Model 124 showed the highest posterior exceedance probability (\( \Phi = 0.0128 \)), but is closely followed by several other models. Based on the Bayesian model selection there was no obvious winning model (Fig. 3A). The post hoc family analysis, where models are grouped by the presence of modulatory effects on the six tremor regions and cerebello-dentato-thalamic pathway, showed quite convincingly that modulatory input on the cerebello-thalamic connections (\( \Phi > 99 \)) was more likely than no input on the cerebello-thalamic connections (Fig. 3B). The thalamus (\( \Phi = 0.74 \)), cerebellar lobule V (\( \Phi = 0.71 \)), SMA (\( \Phi = 0.74 \)) and PMC (\( \Phi = 0.63 \)) were also more likely to be modulated by tremor variation (Fig. 3B). The primary motor cortex (\( \Phi = 0.52 \)) and cerebellar lobule VIII (\( \Phi = 0.45 \)) showed no clear preference for models with or without modulatory input of tremor variation.

Effective connectivity: Bayesian Model Averaging

Modulatory inputs on the six intrinsic and two extrinsic, cerebello-dentato-thalamic, connections were extracted. Modulatory input of tremor variation exhibited a significant excitatory influence on the intrinsic thalamic connections (mean 1.26, SD 0.42, \( P < 0.0000 \)) and cerebellar lobule V (mean 0.32, SD 0.32, \( P = 0.0006 \)) connections, and on the extrinsic connection from cerebellar lobule V to the thalamus (mean 0.82, SD 0.89, \( P = 0.00128 \)). Modulatory input of tremor variation exhibited a significant inhibitory influence on M1 (mean –0.30, SD 0.25, \( P < 0.0000 \)), SMA (mean –0.91, SD 0.27, \( P < 0.0000 \)), PMC (mean –0.55, SD 0.29, \( P < 0.0000 \)) and cerebellar lobule VIII connections.
Results are summarized in Fig. 3C.

There was a significant driving force of task on SMA and PMC (see Supplementary material for full details of endogenous and driving coupling parameters). Furthermore, there was a difference in driving force on the SMA between the motor task with reading versus without reading \( t(34) = 10.79, P < 0.0000 \). There was no difference in driving force between tasks on the PMC \( t(34) = 0.13, P = 0.39 \).

**Functional connectivity results in essential tremor and healthy controls**

In essential tremor patients, the M1 and SMA seeds showed reduced functional connectivity with right cerebellar lobules V and VI compared to healthy controls (Fig. 4A and Table 2). Right cerebellar lobules I–IV, V, VI and VIII seeds all showed reduced functional connectivity with M1 and SMA compared to healthy controls (Table 2).

For the M1 seed, functional connectivity with right cerebellar lobules VI, crus II, vermis VI and lobule VIII, and left cerebellar lobule VIIIb, crus II and lobule VIII, correlated negatively with tremor severity (TRS A + B). For the cerebellar lobule VIII seed, functional connectivity with the primary motor cortex correlated negatively with tremor severity (TRS A + B) (Fig. 4B and Table 3). M1 and cerebellar lobule VIII thus show a reciprocally observed functional disconnection correlated to increasing tremor severity. For the right cerebellar lobule I–IV seed, functional connectivity with the left thalamus correlated positively with tremor severity (TRS A + B) (Fig. 4B and
Figure 4  Decreased cerebellar-cortical functional connectivity in essential tremor. (A) Between-group differences illustrating areas of decreased connectivity in patients with essential tremor compared to healthy controls for the M1, SMA, cerebellar lobule I–IV, V, VI and VIII seeds. (B) Correlation between connectivity and TRS A + B scores for the M1, cerebellar lobule I–IV and VIII seed. Results are projected on the ch2better-template using MRICron. Cluster-wise inference is used ($P < 0.05$ FWE corrected, cluster-defining threshold of $P < 0.001$).
threshold of \( P \) compared to controls (Neely et al. 2015). Findings of decreased cerebello-cortical functional connectivity between cerebellar lobule I–IV and the motor cortex and posterior cerebellum was associated with increased functional connectivity between cerebellar lobule I–IV and the motor thalamus in patients with essential tremor.

**Table 2** Local maxima of group differences in cerebello-cortical functional connectivity

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>( t ) value</th>
<th>( P_{FWE-corr} )</th>
<th>Cluster size</th>
<th>( x ) (mm)</th>
<th>( y ) (mm)</th>
<th>( z ) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls &gt; ET - left M1 seed</td>
<td>Right</td>
<td>4.68</td>
<td>0.0078</td>
<td>86</td>
<td>14</td>
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<td>-13</td>
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<tr>
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<td>3.95</td>
<td>0.0049</td>
<td>128</td>
<td>24</td>
<td>-50</td>
<td>-23</td>
</tr>
<tr>
<td>Cerebellar lobules VI</td>
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<td>3.93</td>
<td>0.0231</td>
<td>43</td>
<td>30</td>
<td>-64</td>
<td>-27</td>
</tr>
<tr>
<td>Controls &gt; ET - left SMA seed</td>
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<td>4.49</td>
<td>0.0366</td>
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<td>-27</td>
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<td>24</td>
<td>-50</td>
<td>-25</td>
</tr>
<tr>
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<td>102</td>
<td>12</td>
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<td>-13</td>
</tr>
<tr>
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<td>128</td>
<td>24</td>
<td>-60</td>
<td>-13</td>
</tr>
<tr>
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<td>0.0269</td>
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<td>12</td>
<td>-74</td>
<td>-25</td>
</tr>
<tr>
<td>Controls &gt; ET - right cerebellar lobule IV seed</td>
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<td>0.0035</td>
<td>85</td>
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<td>-22</td>
<td>49</td>
</tr>
<tr>
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<td>0.0381</td>
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<td>10</td>
<td>15</td>
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<tr>
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<td>0</td>
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<tr>
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<td>45</td>
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<td>-24</td>
<td>49</td>
</tr>
<tr>
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<td>2</td>
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<tr>
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<td>-4</td>
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<td>2</td>
<td>59</td>
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<td>-5</td>
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<tr>
<td>Supplementary motor area</td>
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<td>0.0269</td>
<td>38</td>
<td>12</td>
<td>-74</td>
<td>-25</td>
</tr>
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</table>

Stereotactic coordinates of local maxima of cerebello-cortical functional connectivity in essential tremor patients compared to controls (\( P > 0.05 \), FWE corrected, cluster-defining threshold of \( P < 0.001 \)), coordinates in MNI space. ET = essential tremor.

Table 3). None of the seed regions’ functional connectivities correlated with VAS scores or disease duration.

**Discussion**

This study provides two novel findings that support an important role for the cerebellum, the thalamus, and the cerebello-dentato-thalamic tracts in the pathophysiology of essential tremor. First, the effective connectivity analysis demonstrated a significant excitatory modulating effect of tremor variation on the extrinsic cerebello-dentato-thalamic connection and on intrinsic thalamic and cerebellar lobule V activity. Furthermore, we have replicated and expanded findings of decreased cerebello-cortical functional connectivity, related to a motor task, between the motor cerebellum and cortical motor areas in essential tremor patients compared to controls (Neely et al., 2014). More importantly, decreased functional coupling between the primary motor cortex and posterior cerebellum was associated with an increase in clinically assessed tremor severity during the motor task. Additionally, an increase in clinically assessed tremor severity was associated with increased functional connectivity between cerebellar lobule I–IV and the motor thalamus in patients with essential tremor.

**Altered cerebellar output**

Our findings advocate that modulatory tremor input is associated with activity within the cerebello-dentato-thalamic network. During the motor task, inducing action tremor, all included motor regions exhibited self-inhibiting properties. When incorporating tremor variation during the motor task, intrinsic inhibitory activity of the cortical motor regions and cerebellar lobule VIII increased. However, tremor modulation exhibited an excitatory modulating effect on the cerebello-dentato-thalamic tract, leading from cerebellar lobule V to the thalamus, and intrinsic cerebellar lobule V and thalamic activity. Our results do not give a direct answer as to whether this excitation would give rise to tremor. It is important to note that this excitation does not directly represent a neurophysiological correlate, but is modelled based on the functional MRI and EMG signals. Our results do indicate that cerebello-dentato-thalamic activity is perturbed in essential tremor, which can be placed in a broader framework of evidence regarding the pathophysiology of essential tremor. Previously, GABAergic neurotransmission dysfunction within the cerebellum has been observed, with increased \(^{11}\)C-flumazenil binding to GABA-receptors in the cerebellar
cortex, increasing with tremor severity (Gironell et al., 2012). Pathology studies also show evidence for cerebellar changes, with Purkinje cell loss and axonal swelling (Louis et al., 2007; Rajput et al., 2012; Symanski et al., 2014), and simultaneous remodelling of the cerebellar cortex (Erickson-Davis et al., 2010; Babij et al., 2013; Lin et al., 2014). Purkinje cells from the sole output channel from the cerebellar cortex, and lead to the deep cerebellar nuclei, including the dentate nucleus. GABAergic Purkinje cell synapses constitute the majority of all synapses in the dentate nucleus, with their action strongly regulating the intrinsic activity of the dentate nucleus (Uusisaari and Knöpfel, 2008). Besides pathological changes in the cerebellar cortex, altered dentate nucleus function has been postulated in essential tremor (Boecker et al., 2010; Paris-Robidas et al., 2011; Buijink et al., 2015). Whether the cerebellar cortical pathology is secondary to changes in the dentate nucleus, or vice versa, remains controversial. Altered $^{11}$C-flunazenil binding to GABA-receptors (Boecker et al., 2010) and a decrease in the number of GABA receptors in the dentate nucleus in essential tremor patients (Paris-Robidas et al., 2011) both suggest abnormal functionality of GABA receptors within the dentate nucleus. Electrophysiology data indicate that neurons within the dentate nucleus possess a pacemaker-like activity, with the ability to generate spontaneous inhibitory postsynaptic potentials, which can be increased or decreased depending on GABAergic Purkinje cell input (Jahnsen, 1986). Tremor could consequently result from a disinhibited dentate nucleus and subsequent pathological entrainment of the cerebellar-thalamo-cortical network (Pinault and Deschénes, 1992). This may be explained as a result of loss of GABAergic tone in the cerebellar system (Fig. 5). A recent functional MRI study using a finger-tapping task showed increased activity of the dentate nucleus with increasing clinical tremor severity, in line with this hypothesis (Buijink et al., 2015).

### Functional integrity of the motor network

Patients with essential tremor demonstrate decreased functional coupling between cerebellar motor areas and cortical motor areas compared to controls during a motor task. Furthermore, a decrease in functional coupling between the primary motor cortex and posterior cerebellum is correlated with an increase in tremor severity. Two recent functional MRI studies using a motor task showed decreased activity of cerebellar motor regions related to a motor task in essential tremor (Neely et al., 2014; Buijink et al., 2015). Increased functional coupling between cerebellar lobule I–IV and the thalamus is correlated with an increase in tremor severity. It is possible that the previously mentioned altered cerebellar output gives rise to changes in cerebello-cortical connectivity. The positive correlation between tremor severity and functional coupling between cerebellar lobule I–IV and the thalamus in patients with essential tremor, together with the excitatory effect of tremor modulation on the cerebellum, cerebellar outflow tracts and the thalamus during the motor task as observed in the effective connectivity analysis, support the idea of pathological entrainment within the cerebellar-thalamic system. In the case of tremor interference, and tremor oscillations throughout the motor network, one would also expect increased cerebello-cortical activity due to entrainment of the cerebell-thalamo-cortical network. However, an EEG-EMG coherence study has shown that cortical involvement in tremor is only intermittent, and therefore does not seem to be a crucial player within the tremor network (Raethjen et al., 2007). Alternatively, perturbed cerebellar output could generate improper thalamic activity and consequently disrupt physiological motor-related connectivity with the motor cortex (Jahnsen, 1986; Pinault and Deschénes, 1992). Our results support the hypothesis that increasing tremor severity

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>t value</th>
<th>$P_{\text{FWE-corr}}$</th>
<th>Cluster size</th>
<th>x (mm)</th>
<th>y (mm)</th>
<th>z (mm)</th>
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<tbody>
<tr>
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<td>TRS A + B</td>
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<td>5.98</td>
<td>0.0003</td>
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<td></td>
<td></td>
<td>−6</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td>4</td>
<td>−80</td>
<td>−35</td>
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<td>3.66</td>
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<td></td>
<td>10</td>
<td>−72</td>
<td>−29</td>
</tr>
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<td>Cerebellar lobule VI</td>
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<td>0.0338</td>
<td>34</td>
<td>16</td>
<td>−56</td>
<td>−27</td>
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<tr>
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<td>TRS A + B</td>
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<td>0.0143</td>
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<td>−6</td>
<td>−22</td>
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<td></td>
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<tr>
<td>ET correlated positively with</td>
<td>TRS A + B</td>
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<td>5.40</td>
<td>0.0429</td>
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</tr>
<tr>
<td>Thalamus</td>
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<td></td>
<td></td>
<td>−10</td>
<td>−28</td>
<td>9</td>
</tr>
</tbody>
</table>

*Table 3 Local maxima of cerebello-cortical functional connectivity correlated with tremor severity (P > 0.05, FWE corrected, cluster-defining threshold of $P < 0.001$), coordinates in MNI space. ET = essential tremor.*
proporionally disrupts cerebello-cortical connectivity. Moreover, continuous increased input from the dentate nucleus via the thalamus could cause amplification of inhibitory mechanisms within the cerebral cortex. Inhibitory circuits within the motor cortex are reported to be aberrant and less modifiable in essential tremor (Chuang et al., 2014). In addition, increased 11C-flumazenil binding to GABA-receptors has also been found in the ventrolateral thalamus and lateral premotor cortex in essential tremor (Boecker et al., 2010).

**Differential involvement of the anterior and posterior cerebellum in essential tremor**

The anterior cerebellum is formed by lobules I to V/VI, and is divided by the primary fissure from the posterior cerebellum, formed by lobules VI/VII to X (Herrup and Kuemerle, 1997; Eisenman, 2000). Interestingly, to our knowledge, the anterior and posterior cerebellum, although both involved in motor control, are not discussed separately in essential tremor research, even though the physiological, developmental and genetic properties of each are quite different (Herrup and Kuemerle, 1997; Eisenman, 2000; Witt et al., 2009). Our functional and effective connectivity results suggest that both the anterior and posterior cerebellum are involved in essential tremor. There is, however, a discrepancy in reduced functional connectivity between M1 and the posterior cerebellum associated with increasing tremor severity, and an apparent lack of this reduced functional connectivity between M1 and regions within the anterior cerebellum. On the other hand, an excitatory modulatory effect of tremor was observed in cerebellar lobule V (anterior cerebellum) and on the connections between cerebellar lobule V and the thalamus. We currently have no clear explanation for this observed difference. Although this discrepancy could be due to insufficient sample size, for future pathology studies, it would be of interest to divorce the involvements of the anterior and posterior cerebellum by assessing them separately.

**Methodological considerations**

A known and persistent problem with functional MRI studies is their limited temporal resolution. This makes the identification of a tremor generator challenging. However, it is a useful technique for studying properties of regions within the cerebello-thalamo-cortical network, especially when combined with EMG recordings. This is the first time EMG signals were incorporated in a DCM analysis. It needs to be stressed that the residual EMG regressor is not the EMG signal as recorded from the muscle. It is a reflection of the waxing and waning EMG signal with respect to the task, i.e. the involuntary movements, and does not necessarily say something about clinical severity. Further studies using electrophysiological techniques may be required to provide deeper insights into the synaptic mechanisms involved. Although our results appear robust, they will need to be replicated in the future. For this study, the parameters characterizing the cerebello-thalamic connections were chosen as indirect measures to assess the possible involvement of the dentate nucleus and the cerebelldentato-thalamic tract in essential tremor. These connections represent the net effect of the cerebello-dentato-thalamic tracts. No tremor-related activity was observed in the dentate nucleus in individual subjects, possibly due to the high iron-content of the dentate nucleus and resulting low signal-to-noise ratio of its blood oxygen level-dependent signal (Diedrichsen et al., 2011). To be able to include the dentate nucleus in future models, studies with a higher spatial and temporal resolution are warranted to reproduce our observed excitatory effect on the cerebello-dentato-thalamic pathway.

A common difficulty in functional imaging studies lies in selecting a suitable task for healthy controls that corresponds well with the patients’ task. For this study, a mimicked tremor was chosen. Consequently, the two groups were actually performing a qualitatively different task. These tasks were chosen to allow optimal distinction of brain networks for the functional connectivity analysis, involved in involuntary tremor as opposed to compensation or afferent feedback by deliberate, mimicked tremor movements. However, due to this qualitative difference, for the effective connectivity analysis the patient group was not compared with a healthy control group. Future studies could circumvent this problem by using other techniques such as enforcing passive wrist oscillations as an additional control condition, as has been used previously by Bucher and colleagues (1997). One could then additionally assess whether there are differences within the tremor circuitry in
excitatory and inhibitory connections between patients and healthy controls.

Finally, as mentioned in the ‘Materials and methods’ section, a silent reading task was offered during half of the task blocks, which may have influenced activity within the motor network and could therefore have affected our effective connectivity results. There was a significant difference in driving effect of the two tasks on the SMA and not on the PMC, as observed in the effective connectivity analysis. However, the motor task with silent reading had merely an additional excitatory effect compared to the motor task in which only the command to stretch the right arm was given. We expect that this will not have affected the final conclusions of the effective connectivity analysis.

In conclusion, our findings suggest that cerebello-dentato-thalamic activity and cerebellar-cortical connectivity are perturbed in essential tremor, supporting previous evidence of cerebellar pathology in essential tremor. This perturbed cerebello-dentato-thalamic activity could subsequently affect the rest of the cerebello-thalamo-cortical network, leading to tremor on the one hand and possibly less effective physiological output on the other hand. Investigating effective connectivity changes in essential tremor represents a new avenue of study that may shed light on its underlying pathophysiology.

Acknowledgements
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Supplementary material
Supplementary material is available at Brain online.

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