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Bilateral cerebellar activation in unilaterally challenged essential tremor

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ABSTRACT

Background: Essential tremor (ET) is one of the most common hyperkinetic movement disorders. Previous research into the pathophysiology of ET suggested underlying cerebellar abnormalities.
Objective: In this study, we added electromyography as an index of tremor intensity to functional Magnetic Resonance Imaging (EMG-fMRI) to study a group of ET patients selected according to strict criteria to achieve maximal homogeneity. With this approach we expected to improve upon the localization of the bilateral cerebellar abnormalities found in earlier fMRI studies.
Methods: We included 21 propranolol sensitive patients, who were not using other tremor medication, with a definite diagnosis of ET defined by the Tremor Investigation Group. Simultaneous EMG-fMRI recordings were performed while patients were off tremor medication. Patients performed unilateral right hand and arm extension, inducing tremor, alternated with relaxation (rest). Twenty-one healthy, age- and sex-matched participants mimicked tremor during right arm extension. EMG power variability at the individual tremor frequency as a measure of tremor intensity variability was used as a regressor, mathematically independent of the block regressor, in the general linear model used for fMRI analysis, to find specific tremor-related activations.
Results: Block-related activations were found in the classical upper-limb motor network, both for ET patients and healthy participants in motor, premotor and supplementary motor areas. In ET patients, we found tremor-related activations bilaterally in the cerebellum: in left lobules V, VI, VIIb and IX and in right lobules V, VI, VIIIa and b, and in the brainstem. In healthy controls we found simulated tremor-related activations in right cerebellar lobule V.
Conclusions: Our results expand on previous findings of bilateral cerebellar involvement in ET. We have identified specific areas in the bilateral somatomotor regions of the cerebellum: lobules V, VI and VIII.

1. Introduction

Although essential tremor (ET) is one of the most common hyperkinetic movement disorders (Louis et al., 1998), the underlying disease mechanism is poorly understood. ET has long been considered a benign disorder, but opinions about the disabling nature of ET are changing (Louis and Okun, 2011).

Cerebellar abnormalities are commonly found in investigations of the pathophysiology of ET. Yet, post-mortem studies have provided conflicting results, with cerebellar degeneration reported in some (Louis et al., 2007; Shill et al., 2008) but not all studies (Rajput et al., 2012).

Similarly, neuroimaging results in ET are also incongruent, but do provide support for cerebellar involvement. In structural imaging the most frequent result is cerebellar abnormality in ET, although this is not consistently reported. These reported abnormalities are located in the anterior and posterior lobules of the cerebellum, although not all studies specify the specific areas in the cerebellum (Sharifi et al., 2014). Positron emission tomography experiments consistently report changes in blood flow in the bilateral cerebellum and in some cases in the red nucleus, thalamus and inferior olive during performance of a motor task (Colebatch et al., 1990; Jenkins et al., 1993; Wills et al., 1994). Functional Magnetic Resonance Imaging (fMRI) studies,

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examining motor tasks in ET patients, report abnormalities in widespread areas of in the (bilateral) cerebellum but are not able to point to specific locations due to methodological limitations (Bucher et al., 1997; Neely et al., 2014). Clinically, cerebellar abnormalities would fit well with the presence of symptoms associated with cerebellar malfunction in ET, such as intention tremor (Deuschl et al., 2000; Louis et al., 2009).

Although many of the results point towards the cerebellum, overall studies and especially functional neuroimaging studies, are inconclusive about the specific areas of the cerebellum involved in ET. One cause contributing to this imprecision in findings may be that 'ET' used to be the label for 'tremor not otherwise specified', resulting in a heterogeneous group with high variability in clinical presentation, response to therapeutic intervention and on etiologic level. In this study, we have attempted to define a more homogeneous group of ET patients by requiring a clear diagnosis and in addition a positive response to propranolol medication. We selected propranolol for this study, as it is a drug that has obtained level A evidence for efficacy in ET (Zesiewicz et al., 2005).

Moreover, we improved upon existing functional imaging methodology in ET by combining electromyography (EMG) and fMRI. This novel approach allows recording tremor simultaneously with brain activity and to directly relate tremor to brain activity in the analysis. We expected to improve upon the localization of the bilateral cerebellar abnormalities found in earlier fMRI studies.

2. Methods

2.1. Subjects

This study was conducted in two academic hospitals in The Netherlands: the University Medical Center Groningen (UMCG) and the Academic Medical Center in Amsterdam (AMC). Patients who had a definite diagnosis of ET according to criteria defined by the Tremor Investigation Group were included (Bain et al., 2000). All patients had bilateral upper limb tremor, an age at onset <65 years, and a disease duration >5 years. A positive family history was present in most patients (see Table 1) but not required for inclusion. Patients had to report

Table 1
Patients and healthy controls characteristics.

	Age	Sex	Mean tremor frequency (Hz)	Age at onset (years)	Duration (years)	Family history	Head tremor	Alcohol response	Propranolol use (mg)	TRS-score off medication	VAS-score off medication
Patients											
1	21	Male	10	10	11	+	−	+	40	15	5.4
2	22	Male	7	12	10	−	−	+	20	13	5.2
3	27	Male	7.5	0	27	−	−	+	160	22	8.7
4	30	Female	8	15	15	+	−	?	20	17	2.9
5	32	Female	7	3	29	+	−	+	40	22	6
6	35	Male	8	7	28	+	−	?	80	17	7.8
7	46	Male	7.5	5	41	+	−	+	80	19	4.4
8	47	Male	7	15	32	+	−	+	40	15	6
9	48	Female	7	10	38	+	+	−	120	37	5.4
10	53	Female	7.5	28	25	+	+	+	30	35	7.8
11	53	Male	8	16	37	+	−	+	50	19	8.6
12	57	Female	7	22	40	+	+	?	10	23	4
13	62	Female	8.5	5	57	+	−	?	100	36	8.5
14	63	Male	7	43	20	+	−	+	40	17	3.4
15	63	Female	7.5	39	24	+	−	+	80	29	7.4
16	64	Male	6.5	12	52	+	−	+	20	17	4
17	65	Female	7.5	60	5	+	+	?	80	20	2.7
18	69	Male	7.5	40	29	+	+	−	40	45	9.2
19	72	Male	6	10	62	+	+	+	320	48	9.2
20	74	Male	9	50	24	−	−	?	80	32	6.6
21	80	Female	6	60	20	+	−	+	80	41	6.9
Mean (SD)	51.6 (17.8)	M: 12 F: 9	7.5 (0.9)	22 (18.9)	29.8 (15)				72.9 (67.8)	25.7 (10.8)	6.2 (2.1)
HC											
1	20	Male	5								
2	22	Male	3.5								
3	27	Male	5								
4	30	Female	5								
5	33	Female	3.5								
6	36	Male	7.5								
7	47	Male	6								
8	49	Male	4								
9	52	Male	6.5								
10	52	Male	4								
11	56	Male	3.5								
12	57	Female	6								
13	59	Female	5								
14	59	Female	4								
15	60	Male	5.5								
16	60	Female	4								
17	62	Male	4.5								
18	68	Male	5.5								
19	68	Male	5.5								
20	72	Female	7								
21	74	Male	6								
Mean (SD)	50.6 (16.4)	M: 14 F: 7	5.1 (1.2)								

VAS: Visual Analog Scale, range 0–10. TRS: Tremor Rating Scale, range 0–88. SD: standard deviation.