Diagnosis and imaging of essential and other tremors

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CHAPTER 6

INCREASED CEREBELLAR ACTIVATIONS DURING GOAL-DIRECTED MOVEMENT IN ESSENTIAL TREMOR: AN FMRI STUDY

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ABSTRACT

INTRODUCTION: Abnormalities in goal-directed movement are an important symptom of essential tremor (ET), and are clinically related to cerebellar disease. The current study aims to examine how these movements are associated with abnormal brain activity in ET patients.

METHODS: Nineteen ET patients and seventeen healthy participants performed a goal-directed movement task using an MR-compatible wrist device. Spatial coordinates of participants' movements were recorded during scanning and used to calculate reaction times and variability in movement paths. The target stimuli that prompted participants to move were incorporated in an event-related fMRI design, to correlate the goal-directed movements with cerebral activity. Disease severity, disease duration, intention tremor (assessed clinically with finger-to-nose manoeuvres) were used as clinical covariates in separate analyses.

RESULTS: ET patients were affected mildly (off-medication median Tremor Rating Scale score 22 (range 13-45)). We found no significant difference in reaction time or variability in movement paths between patients and healthy participants. We found increased activations in cerebellar vermis 4/5/6 in ET patients (T=5.11, coordinates in MNI space x=3, y=-63, z=-5), when comparing back-to-centre movements versus baseline. There was no correlation between brain activation during the goal-directed movement task and any of the clinical covariates in ET patients.

DISCUSSION: We report increased cerebellar activation in mildly affected ET patients during goal-directed movements, in the absence of differences in task performance compared to healthy participants. These results extend on earlier reports of increased cerebellar activation during postural tasks, and lend further support to the notion of underlying cerebellar abnormalities in ET.

INTRODUCTION

Essential tremor (ET) is the most common tremor disorder, and is characterized by bilateral action tremor of the hands and forearms (1, 2). The tremor occurs during action and posturing, and apart from the hands and arms, the voice, head and more infrequently jaw, tongue, legs and feet can also be affected (3). ET often runs in families, and half of the patients claim their tremor is reduced by the intake of one or two glasses of alcohol.

A feature that is common in ET, but atypical in most other tremor disorders, is intention tremor: tremor worsening during goal-directed movement (4-6)(see also Chapter 2). Intention tremor is considered to be a sign of cerebellar disease (4), and apart from ET, it is also seen in multiple sclerosis (7) and Holmes (rubral) tremor (8): diseases that affect the cerebellum or cerebellar outflow-tract. Therefore, the occurrence of intention tremor in ET fits well with the emerging pathophysiological view of ET as a cerebellar disease (9, 10). Likewise, in support of the cerebellar hypothesis, there is increasing acknowledgement of ataxia in ET. Several studies have shown signs of mild ataxia in ET patients, such as mild gait ataxia (11-13), hypermetria (4, 14), and drawing ataxia (15). These clinical signs and symptoms lend further support to the notion of underlying cerebellar abnormalities.

Neuroimaging studies also provide evidence for cerebellar involvement in ET (16). Two published motor fMRI-studies both demonstrated abnormal cerebellar activity in ET (17)(see also Chapter 4). However, the movement tasks investigated in these studies did not extend beyond a comparison between posturing of the tremulous arm versus rest. As abnormalities in intentional movement are an important clinical symptom of ET, the current study aims to examine how goal-directed movement is associated with abnormal brain activity in the cerebellum and other brain regions in ET patients. Goal-directed movements can be executed and measured in the MRI scanner by employing a centre-out steptracking task and an MR-compatible wrist device (18). Recently, attention has been paid to the effect of deep brain stimulation (DBS) on reach-to-grasp movement in severely affected ET patients (19, 20). DBS of the subthalamic area reduced ataxia especially, returning upon suprathreshold stimulation, leading the authors to hypothesize on the roles of different cerebellar networks in goal-directed movement in ET. We set out to extend on this work by using a goal-directed movement task suitable for fMRI-scanning, thus enabling a link between behavioral and cerebral or cerebellar abnormalities.

METHODS

PARTICIPANTS

The Medical Ethics Committee of the University Medical Center Groningen approved the neuroimaging study of which this study is a subpart. Participants took part after providing informed consent in accordance with the declaration of Helsinki (21). We included patients who had a definite diagnosis of ET according to the TRIG criteria (1): all patients had bilateral upper limb action tremor in the absence of other neurological signs, and disease duration had to be >5 years. Additionally, age at onset was required to be <65 years, thereby excluding late-onset 'senile' ET, which may have a different pathophysiology (2). Patients who took medication for their tremor quit their medication minimally three days before testing. Patients and healthy, age- and gender-matched participants were all right-handed as assessed by the Annett Handedness scale (22). All participants had to score >25 on the Mini Mental State Examination (23) to ensure proper understanding of the task. Exclusion criteria were neurological comor-

bidity (for patients: other than ET), the use of medication affecting the central nervous system, and MR-related contra-indications such as claustrophobia, ferromagnetic implants or pregnancy.

CLINICAL ASSESSMENT OF TREMOR

Tremor was assessed off-medication using the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) (24) parts A, (assessment of tremor amplitude during standardized postures and movements), B (tremor-inducing tasks), and C (a structured interview about limitations in daily life due to tremor). The examination was recorded on video and supplemented with the corresponding spiral drawings. An experienced movement disorders specialist (Dr. J.D. Speelman, AMC) scored TRS parts A and B based on this material. Part C was assessed by vd Stouwe for all patients. Subjective tremor severity was documented using 10 cm visual analogue scales (VAS) ranging from 0: 'no tremor at all' to 10: 'worst tremor imaginable', on which patients marked their scores. Intention tremor was assessed clinically by scoring presence or absence of intention tremor during finger-to-nose manoeuvres, and this score was used as a clinical covariate in the fMRI analysis later on. Scoring of intention tremor was done clinically because the rapid wrist movements within the employed step-tracking task are too brief to detect any tremor, making it impossible to assess intention tremor during task performance.

EXPERIMENTAL SET-UP

Participants performed the task with the right hand, using an MR-compatible manipulandum: a joystick-like device that can rotate in two planes allowing all combinations of wrist flexion-extension and ulnar-radial deviation (Figure 6.1A-C). To provide visual feedback on task performance, angular displacement was measured in both (X and Y) planes by potentiometers mounted in-line with the axes of the manipulandum rings and displayed as a cursor (a 5 x 5 mm square) following digitization using a Power 1401 analog-to-digital converter controlled using Spike 2 (Cambridge Electronic Design (CED), Cambridge, UK). Data were recorded simultaneously at a sampling rate of 100 Hz. During scanning, performance was visually monitored on a second computer in the MR control room.

STEP-TRACKING TASK

Participants were asked to place their cursor in a centre box (3 x 1.5 cm open rectangle) at the start of the experiment. After two seconds, the centre box disappeared and a target stimulus (3 x 1.5 cm open rectangle)

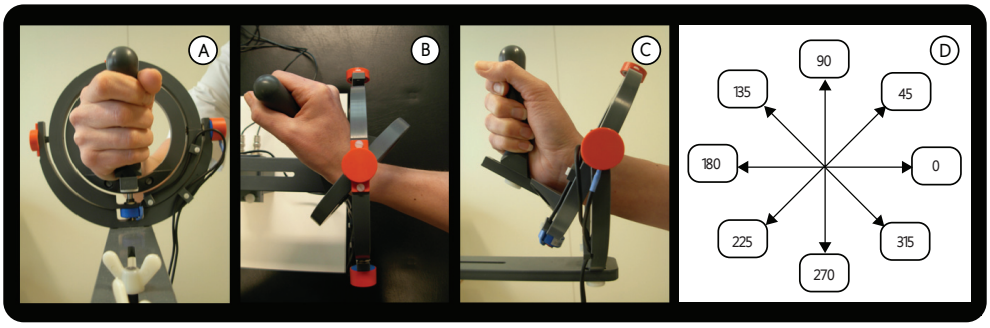

Figure 6.1. MR-compatible wrist device is shown with A) hand held in neutral position, B) wrist extension and C) radial deviation. D) Schematic overview of movement task consisting of 8 different out-of-centre movements. Out-of-centre stimuli appear randomly, and are always followed by a back-to-centre movement.

appeared at one of eight possible positions (Figure 6.1D). Participants were instructed to move towards the target as quickly as possible, and subsequently hold the cursor in the target box until it disappeared (three seconds after appearance), after which they returned to the reappeared centre box. Each entire (outward-inward) step-track trial lasted 5 seconds. After every 10 step-track trials, there was a short break of 4 seconds. One step-track block consisted of 40 out-of-centre and 40 back-to-centre stimuli, 5 for each of the 8 different directions presented in fixed randomised order (randomised but in the same order for every participant). The time intervals between appearances of the stimuli were randomised (jitter: 0.8 s +/- 0.4 s). The entire task consisted of four blocks, totalling 320 stimuli, with 30 seconds of rest in-between blocks.

ANALYSIS OF REACTION TIME

Kinematic data was further analysed using Matlab (Matlab R2013, Mathworks, Natrick, USA). In-house developed software was used to determine reaction time (RT) for each movement in a semi-automatic way. Movement onset was defined as the first time point where the derivative of the smoothed distance vector exceeded 0.02. Initial automatic definitions were checked manually and corrected, if necessary. When no apparent movement was present in the traces, the corresponding stimulus was not used as an event in the fMRI-analysis. Mean reaction time per movement direction per participant was calculated and exported to be analysed in SPSS.

ANALYSIS OF VARIABILITY IN MOVEMENT PATHS

As differences in task execution between groups may induce differences in BOLD activation, we tested for differences in variability in movement execution by applying an approach similar to an analysis employed in earlier studies (19, 20). Since in healthy people recurrent movements are characterized by low variability in movement execution, the deviation from a participants' own average movement trajectory while performing the goal-directed movement task was chosen as a measure to quantify movement execution variability. To do so, we first computed the mean movement trajectory for each participant per type of movement, resulting in 8 mean out-of-centre movement trajectories, and 8 mean back-to-centre movement trajectories. Subsequently, we calculated the distance participants deviated from their personal mean trajectory per trial, and derived the mean deviation for each of the 16 types of movements. Note that this assessment of movement paths may capture ataxic performance, referring to abnormal, uncoordinated movement, but not to hypermetria (overshoot) per se.

STATISTICS

Baseline participant characteristics were compared between groups using Chi-square tests for categorical data (gender), and Kruskal-Wallis tests for non-normally distributed data (age) in SPSS 22 (IBM, Chicago, IL). Normality of distributions was tested using the Shapiro-Wilk test. When log transformation resulted in a normal distribution, mixed design ANOVAs were employed to assess whether RT and variability in movement execution differed between groups.

MRI CHARACTERISTICS

fMRI data acquisition was performed using a 3 Tesla Magnetic Resonance System (Philips, Best, The Netherlands) with a 32-channel head coil. T2*-weighted, 3D functional images were obtained using multislice echo planar imaging (EPI) with an echo time (TE) of 30 ms and a repetition time (TR) of 2000 ms. Per TR 39 axial slices,

with a field of view (FOV) of 224 mm, flip angle of 5° with a 64 X 64 matrix and isotropic voxel size of 3.5 x 3.5 x 3.5 mm were acquired. To provide anatomical information, additional T1-weighted 3D anatomical scans with an axial orientation, a matrix size of 256 x 256 mm and isotropic voxel size of 1 x 1 x 1 mm were obtained.

FMRI ANALYSIS

fMRI data was analysed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.uck.ac.uk/spm). Pre-processing consisted of realignment to correct for individual participant movement, and coregistration to align all functional data to each participant's anatomical scan. A group-specific anatomic template was created (for patients and healthy participants together) with DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (25)) to take age-related changes in anatomy into account, and achieve a more precise inter-subject alignment. Individual functional data were normalized and smoothed using the DARTEL template and a 4-mm full-width half maximum (FWHM) Gaussian kernel. We chose a 4 mm kernel because we were particularly interested in cerebellar (i.e. subcortical) activations, where the effect of a larger 8 mm kernel can be unfavourable (26). To reduce movement artefacts, the six movement parameters derived from realignment corrections were entered as covariates in each participant's analysis. The stimulus onsets derived from the Spike log-file were added to the design as events. This was done separately for out-of-centre and back-to-centre stimuli, because we speculated that differences might exist between these two types of movement, due to the predictable location of the back-to-centre stimuli. Each single-participant first-level model thus consisted of a regressor representing out-of-centre events, a regressor representing back-to-centre events, and the six movement regressors. Subsequently, second level within- and between group comparisons were made on whole brain level. Contrasts were initially thresholded at a voxel level of $p<0.001$, uncorrected, applying a cluster size of 20 voxels. Activations were then considered significant at a cluster corrected p-level <0.05, FWE-corrected.

To test whether brain activations correlated with clinical characteristics in our patient group, we employed Statistical non-Parametric Mapping (version 13b, http://www.sph.umich.edu/ni-stat/SnPM/, 10.000 permutations). We built separate contrasts with presence of intention tremor (scored clinically as either absent or present), disease duration and disease severity (total TRS score) as covariates. Cluster-wise inference was used ($p<0.05$ FWE-corrected, cluster-forming threshold $p<0.05$ FWE-corrected).

RESULTS

PARTICIPANT CHARACTERISTICS

Nineteen ET patients and seventeen healthy participants participated in this study (see Table 6.1 for patient characteristics). Gender and age distribution did not differ between groups ($p=1.000$ and $p=0.733$, respectively). ET patients had a mean age of 55 years, healthy participants of 56 years. Mean disease duration was 31 years. 89% of patients had a positive family history for tremor, whereas 53% reported a decrease of tremor upon alcohol intake. Sixteen patients were treated with propranolol, with a median dose of 60 mg daily, ranging from 10 tot 160 mgs. One patient was treated with primidon, and two patients did not take any medication for their tremor. Clinically, disease severity varied from mild to severe, with a median TRS score of 22 ranging from 13 to 45 off-medication. Patient-perceived tremor severity, measured with visual analogue scales, also varied from mild to severe with off-medi-

TABLE 6.1. PATIENT CHARACTERISTICS

No.	Age	Gender	Age at onset	Disease duration	Family history	Response to alcohol	Medication	Dose (mg)	VAS (off)	TRS (off)	IT	Ataxia (cm)
1	21	M	10	11	+	+	Propranolol	40	5.4	35	-	2.37
2	27	M	0	27	-	+	Propranolol	160	8.7	22	+	1.25
3	30	F	15	15	+	?	Propranolol	20	2.9	17	-	1.72
4	32	F	3	29	+	+	Propranolol	40	6.0	22	-	1.66
5	35	M	7	28	+	?	Propranolol	80	7.8	17	+	1.30
6	46	M	5	41	+	+	Propranolol	80	4.4	19	+	1.10
7	50	M	35	15	+	+	Propranolol	80	6.8	22	+	1.45
8	53	M	15	38	+	+	Propranolol	20	7.2	14	-	1.07
9	57	M	18	39	+	?	Propranolol	10	2.8	25	-	2.21
10	57	F	22	35	+	?	Propranolol	10	4.0	23	+	1.29
11	62	M	22	40	+	?	None	-	9.4	22	-	1.23
12	64	M	12	52	+	+	Propranolol	20	4.0	17	-	1.00
13	65	M	30	35	+	+	Propranolol	40	4.4	20	-	1.28
14	69	M	40	29	+	-	Propranolol	40	9.2	45	-	1.48
15	70	F	30	40	+	?	Propranolol	80	2.1	13	-	1.81
16	74	M	50	24	-	?	Propranolol	80	6.6	32	+	2.92
17	74	M	20	54	+	+	Primidon	125	2.7	15	+	1.28
18	77	M	50	27	+	?	Propranolol	80	5.4	23	+	1.25
19	80	F	60	20	+	+	None	-	9.2	42	+	2.19
Group	55 ±18	15:5	23 ±17	33 ±12	17:2	10: 1:8	17:2:1	40 iqr 60	5.7 ±2.4	22 iqr 8	9: 10	1.3 iqr 0.55

VAS: visual analogue scale, scored off-medication (range 0-10), TRS: Fahn-Tolosa-Marin Tremor Rating Scale, scored off-medication (parts A-C, range 0-88), IT: intention tremor, iqr: interquartile range. Ataxia: mean value in cm across all movements. Group values: mean ± sd, unless otherwise indicated.

cation scores ranging from 2.1 to 9.4 on a 10-point scale. None of the patients showed tremor at rest, whereas 9 out of 19 patients had intention tremor.

TASK PERFORMANCE

Mean RT was 410 (sd 68) ms in ET patients, and 398 (sd 73) ms in healthy participants. There was no difference between groups (p=0.596). Regarding variability in movement paths, during out-of-centre movements, the median distance to mean movement trajectory was 1.4 cm (interquartile range (IQR) 0.39) in ET patients, and 1.4 cm (IQR 0.36) in healthy participants. For back-to-centre movements, median distance

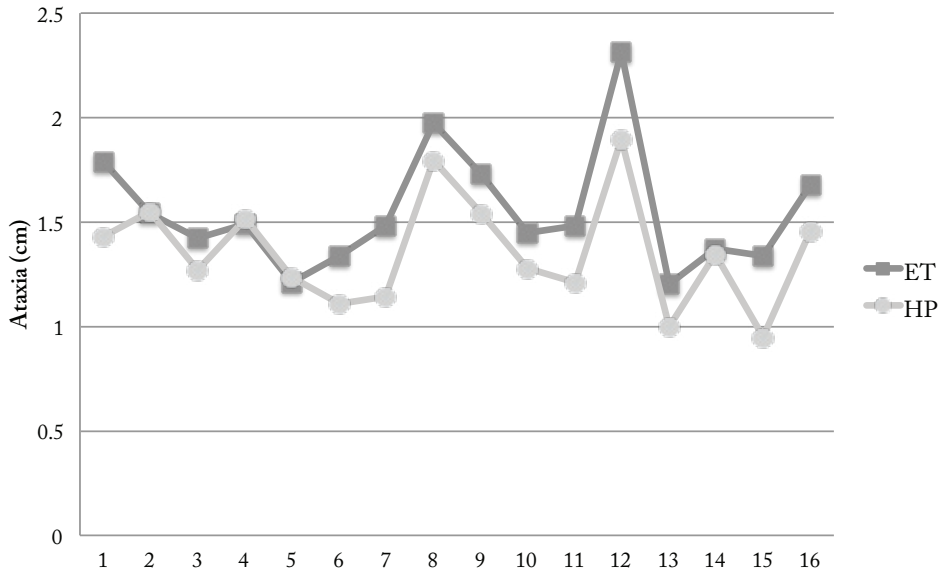

Figure 6.2. Mean variability in movement paths, defined as mean deviation from participants' mean movement trajectory in cm, is depicted for each movement direction. Numbers 1-8 indicate out-of-centre movements; numbers 9-16 indicate back-to-centre movements. ET: essential tremor, HP: healthy participants.

to mean movement trajectory was 1.3 cm (interquartile range (IQR) 0.63) in ET patients, and 1.3 cm (IQR 0.66) in healthy participants. There were no differences between groups (p=0.189)(Figure 6.2).

WITHIN-GROUP FMRI RESULTS

All fMRI results can be found in Table 6.2. For the contrast 'all movements versus baseline', we found cerebral activations in healthy participants in the left premotor cortex, motor cortex, somatosensory cortex and subcentral gyrus. Cerebellar activations were found in the right lobules 4, 5 and 6, and left lobule 6. In ET patients, we found cerebral and cerebellar activations for the contrast 'all movements versus base-line' in the same areas as in the healthy participants, except for the subcentral gyrus and left cerebellar lobule 6.

To check whether differences between the two types of movement exist, we compared brain activations related to out-of-centre movements versus back-to-centre movements directly. In healthy participants, we found increased activations in the left dorsolateral prefrontal cortex, parietal cortex, somatosensory cortex, and anterior cingulate cortex, and in the right secondary visual cortex (V2). For the same contrast ('out-of-centre movement > back-to-centre movement') in ET patients, we found increased activations in the left anterior cingulate and frontal eye fields, and in the right visual cortices (V1-V5), posterior cingulate, occipitotemporal cortex and dorsolateral prefrontal cortex. We found no increased activations for either of the groups for the reverse contrast, 'back-to-centre movements versus out-of-centre movements'.

BETWEEN-GROUP FMRI RESULTS

We found no differences between groups for the contrasts 'all movements versus baseline' and 'out-of-centre movements versus baseline'. For the contrast 'back-to-centre movements versus baseline', we found increased activations in the cerebellum in vermis 6 ex-

TABLE 6.2. SIGNIFICANT FMRI RESULTS FOR ET PATIENTS AND HEALTHY PARTICIPANTS

COMPARISON	LOCATION	CLUSTER SIZE (VOXELS)	T-VALUE	X	Y	Z
All movements: Healthy participants	Motor cortex (BA4), extending into somatosensory cortex (BA3)	146	12.6	-34	-18	52
	Premotor cortex (BA6)	1040	9.68	29	-15	58
	Parietal cortex (BA40/BA5)	1799	10.1	33	-37	46
	Fusiform gyrus (BA37)	339	6.23	51	-67	0
	Subcentral gyrus (BA43)	134	6.15	60	-15	36
	Cerebellum: lobule 6, extending into lobules 4 and 5	2157	9.28	21	-51	-21
	Cerebellum: lobule 6	215	7.32	-22	-51	-24
All movements: ET patients	Premotor cortex (BA6), extending into motor cortex (BA4)	7465	10.56	-2	-10	52
	Somatosensory cortex (BA2/3)	38	8.54	-39	-25	49
	Parietal cortex (BA40/BA3)	456	5.55	36	-36	49
	Fusiform gyrus (BA37)	91	5.07	50	-63	-3
	Cerebellum: lobules 4/5	1650	10.97	15	-51	-21
Out-of-centre movements > back-to-centre movements: HP	Parietal cortex (BA40)	469	7.29	-52	-49	43
	Dorsolateral prefrontal cortex (BA9)	232	7.17	-24	27	37
	Somatosensory cortex (BA3)	95	7.08	-52	-12	34
	Anterior cingulate (BA24)	879	7.49	0	21	37
	Secondary visual cortex (BA18)	180	8.21	20	-67	-8
Out-of-centre movements > back-to-centre movements: ET patients	Anterior cingulate (BA32)	118	6.59	-6	18	42
	Motor cortex (BA4)	95	6.04	-54	6	28
	Dorsolateral prefrontal cortex (BA9)	103	5.85	-26	9	55
	Posterior cingulate (BA23)	128	4.44	8	-28	27
	Occipitotemporal cortex (BA37)	99	5.84	42	-63	6
	Parietal cortex (BA48/40/42/22)	117	6.64	51	-48	28
	Primary visual cortex (BA17)	902	10.08	10	-81	16
	Secondary visual cortex (BA18)	951	8.48	12	-75	-6
	Associative visual cortex (BA19)	272	6.07	26	-72	25
Back-to-centre movements: ET > HP	Cerebellum: vermis 6, extending into vermis 4/5.	118	5.11	4	-66	-8

ET: essential tremor. HP: healthy participants. BA: broadmann area. Voxel-peak level was initially set at $p<0.001$, uncorrected, $k = 30$ voxels. Reported activations correspond with the voxel of maximum activation within clusters of significant activation at $p<0.05$, FWE-corrected. X-, y- and z-coordinates refer to MNI (Montreal Neurology Institute and Hospital) space.

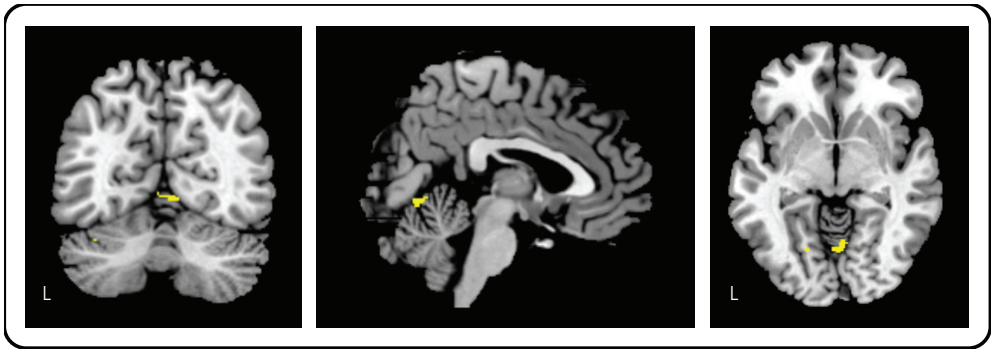

Figure 6.3. Between-group fMRI results: increased activations (SPM T-maps) in ET patients compared to healthy participants in cerebellar vermis lobules 4/5/6 are shown in yellow, for the comparison back-to-centre movements versus base-line. Activations are shown above a clusterwise threshold of $p<0.05$, FWE-corrected. Coordinates of the positions of the three figures are x = 3, y = -63, z = -5 relative to the anterior commissure-posterior commissure plane. L = left hemisphere.

tending into vermis 4 and 5, in ET patients.

CLINICAL COVARIATE FMRI RESULTS

There were no correlations between brain activations in ET patients and presence of intention tremor, disease duration or disease severity.

DISCUSSION

In the current study, we found increased cerebellar activations during goal-directed movement in ET patients compared to healthy participants.

These differences in cerebellar activation were found despite the absence of differences in ataxic performance. We suppose our ET patients performed normally because they were relatively mildly affected: all patients took medication or had no treatment for their tremor, as opposed to the more severely affected cases in other studies in which, for instance, all patients were treated with DBS (19, 20). On that account, we believe our patients represent an earlier disease stage, where patients cannot be distinguished from healthy participants in terms of ataxia. Nonetheless, the fact that we found a difference in brain activation despite the similarities in movement execution makes the cerebral difference even more interesting: the change in brain function may even precede related disease features such as ataxia, and, rather than being related to task performance, may be inherent to ET as a disorder.

In terms of anatomical location, the identified abnormal brain activation is located in a region that is suspected to play a major role in ET pathophysiology (9, 10). At first, it may seem unanticipated that we found increased instead of decreased cerebellar activations, because neurodegeneration, marked by Purkinje cell loss and torpedoes (27, 28), has been reported particularly in the cerebellum including the vermis specifically (29) in ET by some groups. Yet, we may be able to explain our findings by hypothesizing that the cells that are affected in ET are less efficient - being deficient and disorganized – and that this inefficiency may result in increased activations. Another hypothesis would be that the increase in cerebellar activity represents a compensational mechanism for decreased functionality, as our patients performed the task as well as the healthy participants. Moreover, increased cerebellar activations have been reported before dur-

ing simple motor tasks in ET (17)(see also Chapter 4). Why the increased activation is located in the vermal part of lobule 4/5/6 (motor cerebellum) is slightly puzzling, although it has been reported earlier that ET patients have 2-4 times higher torpedo counts in their vermis than healthy subjects (29), indicating that ET involves the spino- as well as the ponto-cerebellum. In the same study, the vermal torpedo count correlated positively with cerebellar hemispheric torpedo count, and with ET cases with head, voice and jaw tremor. Contrarily, in our population, only 1/19 patients had a head tremor, whereas 12/19 patients scored 1/4 points on the TRS' speech item: our patients do not score high on cranial tremor.

It is noteworthy that the difference in brain activation between patients and healthy participants was found specifically for the back-to-centre movements, rather than for out-of-centre or all movements. We speculate this may be because of our task set-up. The peripheral, out-of-centre targets were located quite far from the central target, meaning that participants hardly had to terminate their out-of-centre movement: the movement was terminated because the wrist/device would not allow further outward movement. Contrarily, on the back-to-centre movements, participants had to steer and stop more actively, which might be more demanding as a cerebellar task.
However, when comparing back-to-centre to out-of-centre movements within each group, we did not find any increases in activation, including the cerebellum. For the reverse comparison, out-of-centre versus back-to-centre movements, we found increased activations in the visual cortices, dorsolateral prefrontal cortex, and parietal cortex in both groups. This is probably caused by the fact that the appearance of the next back-to-centre target is predictable (always back to the centre), whereas the up-coming location of the out-of-centre target is unpredictable. The areas where activation was increased can therefore be explained as playing a role in increased visuospatial attention and planning (30-34) for the unpredictable out-of-centre movements.

LIMITATIONS AND STRENGTHS

The fact that our population was in a relatively mild disease stage, where most patients take medication but none would immediately consider deep brain stimulation, can be considered as a limitation to the applicability of our results. It would be interesting to repeat this study in patients in a more advanced disease stage, to see whether the found abnormalities are enhanced.
As mentioned above, it may be considered suboptimal that in our task set-up, we set our out-of-centre targets (too) far from the central target, decreasing the need to accurately terminate movement at these targets. However, this weakness was compensated by the other half of the performed movements, namely the back-to-centre movements, in which there was a need to actively terminate movements.
A strength of our study is the simultaneous measurement of task performance during scanning. By using an MR-compatible device, we were able to study goal-directed movements and their cerebral correlates at the same time.
Moreover, many scientific studies have focused on more severely affected ET patients. Our results can thus be seen as a valuable complimentary effort. The fact that we found cerebellar differences in a less-affected, less-progressed population makes these abnormalities even more distinctive.

CONCLUSION

To conclude, we found increased cerebellar activations related to goal-directed movements in mildly affected ET patients com-

pared to healthy participants, in the absence of differences in movement execution.

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