BRAIN
A JOURNAL OF NEUROLOGY

Altered cortical-cerebellar circuits during verbal working memory in essential tremor

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Essential tremor is a common neurological disorder characterized by motor and cognitive symptoms including working memory deficits. Epidemiological research has shown that patients with essential tremor are at a higher risk to develop dementia relative to age-matched individuals; this demonstrates that cognitive impairments reflect specific, although poorly understood, disease mechanisms. Neurodegeneration of the cerebellum has been implicated in the pathophysiology of essential tremor itself; however, whether cerebellar dysfunctions relate to cognitive abnormalities is unclear. We addressed this issue using functional neuroimaging in 15 patients with essential tremor compared to 15 sex-, education- and age-matched healthy controls while executing a verbal working memory task. To remove confounding effects, patients with integrity of the nigrostriatal terminals, no dementia and abstinent from medications altering cognition were enrolled. We tested whether patients displayed abnormal activations of the cerebellum (posterior lobules) and other areas typically engaged in working memory (dorsolateral prefrontal cortex, parietal lobules). Between-groups differences in the interactions of these regions were also assessed with functional connectivity methods. Finally, we determined whether individual differences in neuropsychological and clinical measures modulated the magnitude of regional brain responses and functional connectivity data in patients with essential tremor. Despite similar behavioural performances, patients showed greater cerebellar response (crus I/lobule VI) compared to controls during attentional-demanding working memory trials ($F = 8.8$; $P < 0.05$, corrected). They also displayed altered functional connectivity between crus I/lobule VI and regions implicated in focusing attention (executive control circuit including dorsolateral prefrontal cortex, inferior parietal lobule, thalamus) and in generating distracting self-related thoughts (default mode network including precuneus, ventromedial prefrontal cortex and hippocampus) (T-values > 3.2; $P < 0.05$, corrected). These findings were modulated by the variability in neuropsychological measures: patients with low cognitive scores displayed reduced connectivity between crus I/lobule VI and the dorsolateral prefrontal cortex and enhanced connectivity between crus I/lobule VI and the precuneus (T-values > 3.7; $P < 0.05$, corrected). It is likely that cerebellar neurodegeneration underlying essential tremor is reflected in abnormal communications between key regions responsible for working memory and that adaptive mechanisms

(enhanced response of crus I/lobule VI) occur to limit the expression of cognitive symptoms. The connectivity imbalance between the executive control circuit and the default mode network in patients with essential tremor with low cognitive scores may represent a dysfunction, driven by the cerebellum, in suppressing task irrelevant thoughts via focused attention. Overall, our results offer new insights into pathophysiological mechanisms of cognition in essential tremor and suggest a primary role of the cerebellum in mediating abnormal interactions between the executive control circuit and the default mode network.

Introduction

Cognitive impairments often accompany typical motor symptoms of essential tremor, one of the most frequent neurological diseases (Louis *et al.*, 1998; MacDonald *et al.*, 2000). A series of neuropsychological studies conducted in patients with essential tremor revealed a broad spectrum of mild cognitive deficits including attention, language and working memory dysfunctions (Lombardi *et al.*, 2001; Troster *et al.*, 2002; Higginson *et al.*, 2008; Kim *et al.*, 2009). Furthermore, epidemiological research has demonstrated that the risk of developing dementia in patients with essential tremor is significantly higher than expected for age; this indicates that cognitive deficits in essential tremor are specific effects associated with the disease and not simply the consequence of ageing (Bermejo-Pareja *et al.*, 2007; Thawani *et al.*, 2009).

Pathophysiological mechanisms underlying essential tremor are still poorly understood. Post-mortem studies found that 8–24% of patients with essential tremor present Lewy bodies within the locus coeruleus and suggested the existence of neurodegenerative processes similar to those described in Parkinson's disease and other parkinsonisms (Louis *et al.*, 2007; Shill *et al.*, 2008; Erickson-Davis *et al.*, 2010; Kuo *et al.*, 2010; Louis, 2010). Although alternative explanations such as cerebrovascular insufficiency or Alzheimer-like mechanisms were also proposed (Elble *et al.*, 2007), pathological research strongly supported the hypothesis that neurodegeneration of the cerebellum is a fundamental disease mechanism (Louis *et al.*, 2007; Shill *et al.*, 2008; Erickson-Davis *et al.*, 2010; Kuo *et al.*, 2010; Louis, 2010). This theory is corroborated by structural neuroimaging studies that demonstrated *in vivo* diffuse grey matter loss within the cerebellum (Quattrone *et al.*, 2008; Benito-Leon *et al.*, 2009; Cerasa *et al.*, 2009); although a single report found no decrease in the cerebellar volume of patients with essential tremor (Daniels *et al.*, 2006). Nonetheless, whether cerebellar alterations relate to cognitive dysfunctions in essential tremor remains a critical open question. Research in patients with focal lesions (strokes or tumours) and functional neuroimaging in healthy subjects have consistently implicated the cerebellum (posterior lobules) in a variety of cognitive functions (Schmahmann, 1996; Desmond and Fiez, 1998; Chen and Desmond, 2005; Schmahmann *et al.*, 2009; Durisko and Fiez, 2010; Marvel and Desmond, 2010); hence, it is probable that cerebellar dysfunctions are at the basis of the cognitive deficits characterizing essential tremor.

It is unlikely, however, that cerebellar dysfunctions *per se* fully explain dementia in essential tremor because the cognitive deficits that have been described in patients with cerebellar lesions are generally mild (Schmahmann, 1996; Desmond and Fiez, 1998; Chen and Desmond, 2005; Schmahmann *et al.*, 2009; Durisko and Fiez, 2010; Marvel and Desmond, 2010).

Functional MRI is a useful technique for exploring brain dysfunctions in neurological disorders and has been successfully employed for characterizing neural networks underlying cognitive impairments in patients with Parkinson's disease and Alzheimer's disease. In particular, a number of studies showed enhanced response of brain regions implicated in episodic memory, executive control and attention in patients with Parkinson's disease and in individuals at risk of Alzheimer's disease, relative to healthy subjects (Bookheimer *et al.*, 2000; Wu and Hallett, 2008; Baglio *et al.*, 2011). These increased activities were interpreted as adaptive responses of dysfunctional brain circuits that maintain normal behavioural performances (Bookheimer *et al.*, 2000; Wu and Hallett, 2008; Baglio *et al.*, 2011). Likewise, a preliminary report from our group demonstrated abnormally enhanced responses of prefrontal and parietal cortices in patients with essential tremor relative to controls, while executing an attentional task compared to a low-level sensory-motor baseline (Cerasa *et al.*, 2010). However, no dysfunctional cerebellar activations were found in essential tremor, probably because we employed a functional MRI task that did not specifically assess cognitive processes based on cerebellar functions.

The aim of the present study was therefore to characterize neural correlates of cognitive dysfunctions in essential tremor using a verbal working memory task that is known to strongly engage cerebellar circuits (Chen and Desmond, 2005). We expected enhanced recruitment of regions implicated in verbal working memory in patients with essential tremor compared to controls. In particular, differences were predicted in the cerebellum (posterior lobules) and other regions of the cognitive cortico-thalamic-cerebellar loop (dorsolateral prefrontal cortex, parietal lobules, anterior cingulate cortex and thalamus) (Chen and Desmond, 2005; Durisko and Fiez, 2010). Furthermore, based on recent findings showing that the white matter fibres connecting cognitive regions may be damaged in essential tremor (Shin *et al.*, 2008; Jia *et al.*, 2010), we explored the functional connectivity between these areas. We hypothesized abnormal functional connectivity of brain regions responsible for verbal working memory in patients with essential tremor relative to

controls. Finally, we determined whether individual differences in the cognitive status of patients with essential tremor, as assessed by a detailed neuropsychological screening, and/or in disease severity, modulated the magnitude of brain responses and/or the functional connectivity data. Given the high heterogeneity of essential tremor, a significant effect of the variability in neuropsychological and clinical measures was expected (e.g. reduced brain responses in individuals with low cognitive scores and/or high disease severity and vice versa).

Participants and methods

Subjects

Fifteen patients with essential tremor (five female, 10 male) and 15 sex-, education- and age-matched healthy controls (eight female, seven male without neuropsychiatric diseases and with normal MRI of the brain) gave their written informed consent to participate in the study that was approved by the Ethics Committee of the University 'Magna Graecia' of Catanzaro in conformity to the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/17c.pdf). None of the patients with essential tremor enrolled in this study had participated in our previous neuroimaging experiments (Quattrone et al., 2008; Cerasa et al., 2009, 2010; Nicoletti et al., 2010). A neurologist (FN), blind to any other result and with 6 years' experience in movement disorders, made the diagnosis of essential tremor according to established criteria (Deuschl et al., 1998). A senior neurologist (AQ), with over 35 years of clinical experience, reviewed and confirmed the diagnosis of all patients with essential tremor. Age at onset, disease duration and severity of tremor, as assessed by the Bain Scale and the Fahn Tremor Rating Scale Part-A, were also collected (Bain et al., 1993; Fahn et al., 1993). Inclusion criteria for patients with essential tremor were: (i) integrity of the nigrostriatal dopaminergic terminals, as evidenced by a normal dopamine transporter scan, to exclude parkinsonisms; (ii) no traumatic brain injury and past or current substance abuse, particularly alcohol; (iii) no dementia according to the DSM-IV (American Psychiatric Association, 1994); in particular, probable Alzheimer's disease was excluded according to the NINCDS-ADRDA criteria (Blacker et al., 1994); (iv) no use of antidepressants, anxiolytics or antipsychotics; (v) 2 weeks off medications for tremor (e.g. benzodiazepines, barbiturates, β-blockers); (vi) right handedness, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971); and (vii) no evident brain lesions, as assessed by a clinical radiologist (FF) with 20 years' experience in neuroradiology, on a standard structural MRI scan.

A trained neuropsychologist (CC) evaluated, in all participants, the following cognitive functions: (i) executive control and flexible behaviour (Frontal Assessment Battery, Modified Card Sorting Test) (Nelson, 1976; Iavarone et al., 2004); (ii) short- and long-term verbal memory (Rey Auditory-Verbal Learning Test) (Rey, 1958); (iii) attention and working memory (Digit Span Forward and Backward) (Wechsler, 1981); (iv) verbal fluency and language comprehension (Controlled Oral Word Association Test, Token Test) (De Renzi and Vignolo, 1962; Benton et al.,

1994); (v) visuospatial skills (Judgement of Line Orientation) (Benton et al., 1978); and (vi) anxiety and depression (Hamilton Rating Scale Anxiety, Beck Depression Inventory) (Hamilton, 1959; Beck and Steer, 1987). The neuropsychological session lasted ~1 h.

Significant differences in demographic and neuropsychological data between groups were calculated using two-tailed, two-sample t-tests within SPSS (Statistical Package for Social Sciences, version 12.0, http://www.spss.it/).

Functional magnetic resonance imaging task

Participants executed a modified version of the Sternberg's verbal working memory paradigm (Desmond et al., 2003; Chen and Desmond, 2005).

Three types of trials were included: (i) high-load working memory: subjects were instructed to remember a string of six uppercase letters presented for 2 s, followed by a 3-s delay with a blank screen. Next, a lowercase probe letter was displayed for 2 s and subjects were asked, within this time window, to press a button when the probe matched any of the letters previously displayed in the string. Alternatively, no response was required. An additional 1-s delay of blank screen concluded the trial that lasted 8 s in total; (ii) intermediate-load working memory: trials were identical to previous ones except for the string that contained three letters intermixed to three abstract symbols (#). The position of letters and symbols within the string was counterbalanced across trials; and (iii) low-load working memory: as before, but the string contained one letter and five symbols.

Four trials of each type were grouped in a block lasting 32 s. The task included 18 blocks (six high-, six intermediate- and six low-load working memory) alternated, in a pseudorandom order, to six fixation blocks (12 s each) during which subjects passively viewed a cross at the centre of the screen (total task duration: 10 min, 48 s). To familiarize with the task design, participants practiced a short version of the paradigm before scanning. This version contained a different set of stimuli from that used during the functional MRI session.

In addition, during the training session, we inspected whether patients with essential tremor presented systematic variations of head tremor amplitude across trials (e.g. increasing of tremor during high-load and decreasing of tremor during low-load working memory trials or vice versa); this was not the case. Nonetheless, we did not directly measure head tremor and we cannot completely exclude that minor changes in this clinical variable may have affected the results.

Stimuli were projected onto a back projection screen throughout a LCD video-projector while reaction times and responses for each trial were recorded via a MRI-compatible fibre optic button box response controlled by LabVIEW (National Instruments, http://www.ni.com/labview/i/).

Reaction time and accuracy mean values for each block were calculated for all participants and entered in ANOVA within SPSS that investigated: (i) the main effect of group (patients with essential tremor, controls); (ii) the main effect of task (high-,

intermediate- and low-load working memory); and (iii) the Group × Task interaction.

Image acquisition and preprocessing

Functional MRI scanning was performed on a 3 Tesla unit with an eight-channel head coil (Discovery MR-750, General Electric). Head movements were minimized using foam pads around the participants' head. Furthermore, subjects displaying head movements >2 mm were excluded from the analyses. Whole-brain data were acquired with echo planar images sensitive to the blood oxygenation level-dependent contrast (35 axial slices, 3-mm thickness each; repetition time = 2000 ms; echo time = 30 ms; voxel size: 3 × 3 × 3 mm).

First, data were preprocessed using whole-brain methods within SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Echo planar images were realigned to the first scan by rigid body transformations to correct for head movements, then normalized to the echo planar images standard template in the Montreal Neurological Institute (MNI) space using linear and non-linear transformations and finally smoothed with a Gaussian kernel of full width at half maximum of 8-mm. Second, we also preprocessed the data using the Spatially Unbiased Infra-Tentorial (SUIT) normalization procedure (http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit_fMRI.htm) that is known to have a more accurate intersubjects alignment of the cerebellar structures compared to whole-brain methods.

Functional magnetic resonance imaging analyses of regional effects

These analyses aimed to: (i) identify significant differences between patients with essential tremor and controls in local responses of brain areas involved in verbal working memory; (ii) assess effects of individual differences in clinical and neuropsychological data of patients with essential tremor on brain regional responses for the high- versus low-load working memory contrast; and (iii) obtain reference coordinates to define the source/seed region in the cerebellum for connectivity analyses.

A random effect model was implemented using a two-stage process (first- and second-level) that allows inferences about the general population from which participants are drawn. For each subject we used a general linear model to evaluate regionally specific effects of task parameters on blood oxygenation level-dependent indices of activation (Friston et al., 1994). The model included four experimental factors (high-, intermediate-, low-load working memory trials and fixation baseline). Low frequency signal drift was removed using a high-pass filter (cut-off 128 s) and an autoregressive modelling [AR(1)] of temporal autocorrelations was applied. At the first level, subject-specific contrast images were generated for each working memory condition versus baseline (high-, intermediate-, low-load working memory versus fixation) and for the high- versus low-load working memory contrast. Each of the working memory versus baseline contrast was entered into a second-level general linear model ANOVA to obtain SPM-F maps that investigated: (i) the main effect of group (i.e. patients with essential tremor, controls); (ii) the main effect of task

(i.e. high-, intermediate-, and low-load working memory); and (iii) the Group × Task interaction.

We also tested whether individual differences in clinical and neuropsychological measures within the essential tremor group were correlated with brain responses for the high- versus low-load working memory contrast (multiple regressions analyses). To further exclude that head movements in patients with essential tremor confounded the results, we repeated the analyses including movement parameters as covariates of no interest in the first-level general linear model. Finally, the same statistical models described thus far were also applied to the cerebellar data that were preprocessed with the SUIT normalization method.

Two approaches for thresholding second level maps were applied. First, for a priori hypotheses in regions of interest, the threshold was set at $P < 0.05$, familywise error correction for multiple comparisons in small volumes (small volume correction) (Worsley et al., 1996; Friston, 1997). Cortical and subcortical regions including the anterior cingulate cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, insula, superior parietal lobules, inferior parietal lobules, thalamus, caudate, putamen, pallidum and cerebellum (posterior lobes) were all defined as a priori regions of interest given their critical engagement in verbal working memory tasks (Chen and Desmond, 2005; Chang et al., 2007; Durisko and Fiez, 2010). All regions of interest were defined using MarsBaR that incorporates the 'aal.02' atlas for automatic anatomical labelling (http://marsbar.sourceforge.net/) (Tzourio-Mazoyer et al., 2002). Secondly, we reported other brain regions that were not predicted a priori but met a threshold of $P < 0.001$, uncorrected >10 contiguous voxels.

Functional connectivity analyses

The physiological connectivity between brain regions can vary as a function of the psychological context (Friston et al., 1997). Here, we were interested in the connectivity that was modulated by the context of performing high- versus low-load working memory. This constitutes a psycho-physiological interaction (Friston et al., 1997). We sought to identify target areas for which connectivity with a cerebellar source/seed (left crus I/lobule VI) differed between groups (patients with essential tremor versus controls and vice versa). Crus I/lobule VI was selected as source/seed on the basis of the significant Group × Task interaction that demonstrated abnormally enhanced activity of this region in patients with essential tremor, relative to controls, during high-load working memory (refer to the 'Results' section). Furthermore, we identified target regions for which the connectivity with the source varied as a function of individual differences in clinical and neuropsychological data in patients with essential tremor. We refer to this latter analysis as higher-order psycho-physiological interaction (Passamonti et al., 2008, 2009).

For each participant, a sphere of 16-mm diameter was created around the left crus I/lobule VI co-ordinates derived from the Group × Task interaction (Fig. 3 for MNI coordinates). The time-series of the blood oxygenation level-dependent response for each participant was computed using the first eigenvariate from all voxels' time series in the sphere. Next, the blood oxygenation level-dependent time series for each individual was

deconvolved to estimate a neuronal time series for the source/seed, using the psycho-physiological interactions deconvolution parameter in SPM8 (Gitelman *et al.*, 2003). The psycho-physiological interaction regressor was calculated as the element-by-element product of the neuronal time series and a vector coding for the main effect of task (+1 for high-load working memory, −1 for low-load working memory). This product was re-convolved by the canonical haemodynamic response function. The statistical model also included the main effect of the task (high- versus low-load working memory) convolved by the haemodynamic response function, and the source neuronal time series. Subject-specific psycho-physiological interaction models were run and contrast images generated such as the identified target regions were those showing a change in connectivity with the left crus I/lobule VI as a function of performing high- versus low-load working memory. These first-level contrast images were entered into second-level general linear model that assessed: (i) target regions for which functional connectivity with the source/seed (for high- versus low-load working memory contrast) differed between groups (patients with essential tremor versus controls and vice versa) (two-sample *t*-test); and (ii) regions for which functional connectivity with the source/seed (for high- versus low-load working memory) was correlated with individual differences in clinical and neuropsychological measures in patients with essential tremor (higher-order psycho-physiological interaction, multiple regressions).

The same statistical approaches previously described for the analyses of regional effects were used for thresholding second-level connectivity maps (regions of interest: $P < 0.05$, familywise error, small volume correction; other regions: $P < 0.001$, uncorrected, >10 voxels).

Results

Participants

Table 1 summarizes demographic, clinical and neuropsychological characteristics of patients with essential tremor and controls. Groups were matched for sex, age and education. Patients presented a mild form of tremor as testified by: (i) the Bain Scale, a self-report measure assessing difficulties in activities of daily living (mean, SD: 33 ± 7.2); and (ii) the Fahn Tremor Rating Scale Part-A, a clinical evaluation of disease severity (mean, SD: 8.8 ± 4.1). None of the patients with essential tremor displayed cerebellar motor signs such as imbalance or dysmetria.

Patients with essential tremor did not differ from controls on neuropsychological tests investigating flexible behaviour, short-term verbal memory, attention, verbal fluency and visuo-spatial skills (Table 1). However, as also reported in previous studies (Lombardi *et al.*, 2001; Troster *et al.*, 2002; Higginson *et al.*, 2008; Kim *et al.*, 2009), patients with essential tremor displayed statistically significant lower mean scores in cognitive control (Frontal Assessment Battery), long-term verbal memory (Rey Auditory-Verbal Learning Test—Delayed Recall) and language comprehension (Token Test) (Table 1). A further assessment of individual data revealed that: (i) 8/15 patients with essential

tremor and 0/15 controls scored below the normative values of the Frontal Assessment Battery (Appollonio *et al.*, 2005); (ii) 2/15 patients with essential tremor and 0/15 controls scored below the normative values of the Rey Auditory-Verbal Learning Test—Delayed Recall (Carlesimo *et al.*, 1996); and (iii) neither patients with essential tremor nor controls scored below the normative values of the Token Test (Spinnler and Tognoni, 1987). Hence, executive dysfunctions were relatively more frequent in patients with essential tremor compared to controls while between-group differences in other cognitive domains (long-term verbal working memory and language comprehension) mainly occurred within the range of normal values. This implies that executive dysfunctions, although mild, may have played a significant role in explaining brain abnormalities detected in our sample of patients with essential tremor. Finally, no differences between groups were found in anxiety and depression (Table 1).

Functional magnetic resonance imaging behavioural performances

Figure 1 displays means ($\pm$SD) of reaction time and % accuracy in patients with essential tremor and controls. We found a significant main effect of the task for reaction time and accuracy ($F = 16.1$, $P < 0.0001$; $F = 45.8$, $P < 0.0001$, respectively), although there was no main effect of group for either measures ($F = 0.8$, $P = 0.7$; $F = 0.4$, $P = 0.84$, respectively) neither a Group × Task interaction ($F = 0.9$, $P = 0.91$; $F = 2.4$, $P = 0.12$, respectively).

Overall, these results demonstrate that increased working memory load was associated with lengthened reaction time and decreased accuracy and that both these effects were similar in patients with essential tremor and controls.

Functional magnetic resonance imaging regional effects

The ANOVA exploring the main effect of group did not identify significant activations in any brain region including our *a priori* regions of interests (regions of interest: $P < 0.05$, familywise error, small volume correction; other areas: $P < 0.001$, uncorrected, >10 contiguous voxels).

The ANOVA investigating the main effect of task revealed several areas that showed either an enhancement or a reduction of their activity as a function of increasing working memory load (F-values > 10, P-values < 0.001, familywise error whole-brain correction or small volume correction). In particular, dorsolateral prefrontal cortex, parietal lobules, anterior cingulate cortex, insula, basal ganglia and cerebellum (posterior lobes) displayed a significant increase of their responses as a function of working memory load (Fig. 2). In contrast, precuneus/retrosplenial cortex and ventromedial prefrontal cortex showed the opposite pattern (decreasing activity as a function of increasing working memory load) (Fig. 2).

More importantly, a significant Group × Task interaction in the left cerebellum (crus I/lobule VI; MNI local maxima: x −12, y −72, z −32, $F = 8.8$, $P < 0.05$, familywise error, small volume correction) and, at a lower statistical threshold, on the right side

Table 1 Demographic, clinical and neuropsychological characteristics of participants included in the study

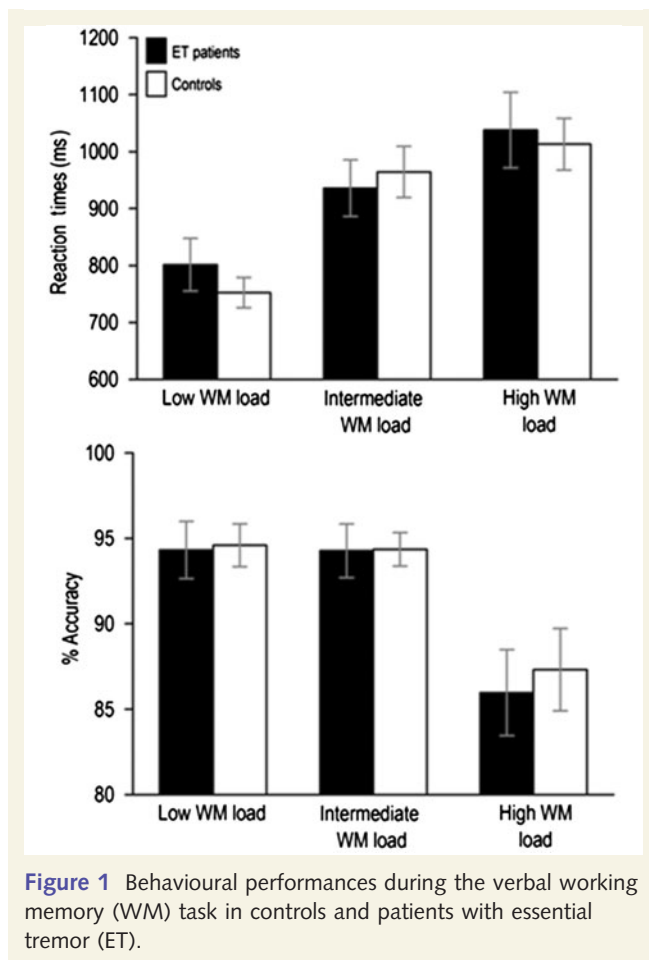| Demographic and clinical data	Patients with essential tremor (n = 15) Mean (SD)	Controls (n = 15) Mean (SD)	Two-sample t-tests	
			T-values	P-values*
Demographic measures				
Age (years)	61.6 (9.3)	60.4 (7.3)	0.3	0.7
Education (years)	9.8 (3.5)	9.3 (4.2)	0.3	0.7
Clinical measures				
Age at onset (years)	45 (15.5)	–	–	–
Disease duration (years)	16.6 (15.4)	–	–	–
Bain scale	33 (7.2)	–	–	–
Fahn-TRS	8.8 (4.1)	–	–	–
Neuropsychological data				
Global cognitive functions				
MMSE	27.4 (2.2)	28.3 (1.8)	1.2	0.2
Executive control				
FAB	13.6 (1.9)	15.2 (1.7)	2.3	<0.03
Flexible behaviour				
MCST (CA)	5.2 (1.5)	5.6 (1.1)	0.6	0.5
MCST (PE)	1.6 (2.4)	1 (1.8)	0.7	0.4
Short-term verbal memory				
RAVLT (IR)	39.6 (5)	42.1 (6.3)	1.1	0.2
Long-term verbal memory				
RAVLT (DR)	6.9 (2.8)	8.8 (1.8)	2.1	0.05
Attention				
Digit span forward	5.5 (0.8)	5.6 (0.8)	0.4	0.6
Digit span backward	3.5 (0.9)	3.7 (0.7)	0.6	0.5
Verbal fluency				
COWAT	23.2 (9.4)	26.6 (8.8)	1.0	0.3
Language comprehension				
Token Test	30.5 (1.9)	32.1 (1.3)	2.6	<0.02
Visuospatial skills				
JLO	22.3 (5)	22.9 (4.7)	0.3	0.7
Anxiety				
HAM-A	8.7 (5.5)	9.6 (6.5)	0.3	0.6
Depression				
BDI	6.6 (4.8)	8.2 (6.2)	0.7	0.4

*P-values reported are uncorrected for multiple comparisons.
BDI = Beck Depression Inventory; CA = correct answers; COWAT = Controlled Oral Word Association Test; DR = delayed recall; FAB = Frontal Assessment Battery; Fahn-TRS = Fahn Tremor Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; IR = immediate recall; JLO = Judgement of Lines Orientation; MCST = Modified Card Sorting Test; MMSE = Mini-Mental State Examination; PE = perseverative errors; RAVLT = Rey Auditory Verbal Learning Test.

(MNI local maxima: x −10, y −70, z −34, $F = 6.3$, $P < 0.003$, uncorrected) was found (Fig. 3). As shown in Fig. 3, the Group × Task interaction was mainly driven by abnormally enhanced activity of crus I/lobule VI in patients with essential tremor relative to controls when performing high-load working memory trials. Two additional regions showed a similar effect: the left thalamus and the right caudate (MNI local maxima for the thalamus: x −19, y −26, z 14, $F = 8.6$, $P < 0.05$, familywise error, small volume correction; MNI local maxima for the caudate: x 20, y 22, z 6, $F = 7.6$, $P < 0.05$, familywise error, small volume correction).

When assessing whether individual differences in clinical or neuropsychological data modulated brain responses in patients with essential tremor (for the contrast high- versus low-load working memory) we found that: (i) scores on a measure of cognitive control (Frontal Assessment Battery) were positively correlated with neural activity of right and left lobule VI and other regions (Fig. 4, Supplementary Table 1); and (ii) disease severity (Fahn Tremor Rating Scale) was negatively correlated with responses of right lobule IV-V, left lobule VI and other areas (Supplementary Fig. 1A, Supplementary Table 2). Of note, similar results to those reported thus far were obtained when including the movement parameters as covariate of no interest in the first-level analyses (Supplementary Material). In addition, when employing the SUIT normalization, more diffuse activations in the left cerebellar hemisphere were detected in comparison to whole-brain methods, in particular, for the Group × Task interaction (Supplementary Material).

Figure 1 Behavioural performances during the verbal working memory (WM) task in controls and patients with essential tremor (ET).

Functional connectivity results

First, we examined whether functional connectivity (for the contrast high- versus low-load working memory) between the cerebellar source/seed and brain target regions was significantly different between groups (controls > essential tremor and vice versa). Comparing controls to patients with essential tremor revealed significantly different coupling between left crus I/lobule VI and regions belonging to the executive control circuit (dorsolateral prefrontal cortex, inferior parietal lobules, thalamus) and the default mode network (precuneus cortex, ventromedial prefrontal cortex, hippocampus) (two-sample t-test, Fig. 5, Supplementary Table 3). The inverse contrast (essential tremor > controls) did not reveal any brain region (no supra-threshold voxels at $P < 0.001$, uncorrected, >10 contiguous voxels) (two-sample t-test).

Secondly, for the analyses exploring higher-order psychophysiological interaction in patients with essential tremor, individual differences in cognitive control (Frontal Assessment Battery scores) significantly modulated the connectivity between the source/seed and dorsolateral prefrontal cortex/ventrolateral prefrontal cortex and between source/seed and precuneus, when performing high- versus low-load working memory (Fig. 6, Supplementary Table 4). In the first case, Frontal Assessment

Battery scores were positively correlated with functional connectivity data, ranging from negative values in low- to positive values in high-Frontal Assessment Battery individuals (Fig. 6A). In contrast, functional connectivity between source/seed and precuneus was negatively correlated with Frontal Assessment Battery scores (positive values in low- and negative values in high-Frontal Assessment Battery subjects) (Fig. 6B). Finally, variability in disease severity (Fahn Tremor Rating Scale) was negatively correlated with functional connectivity between the source/seed and ventrolateral prefrontal cortex (Supplementary Fig. 1B, Supplementary Table 5).

Discussion

Our study is highly significant in exploring core brain mechanisms underlying verbal working memory in essential tremor. Converging results from different approaches (analyses of regional activity, effects of variability in neuropsychological and clinical data on neural responses, connectivity methods) demonstrated a variety of brain dysfunctions in patients with essential tremor that included: (i) abnormally enhanced cerebellar response (crus I/lobule VI) during high-load working memory trials; (ii) altered functional connectivity between crus I/lobule VI and the executive control circuit as well as the default mode network; and (iii) strong modulation of these effects by individual differences in neuropsychological and clinical measures.
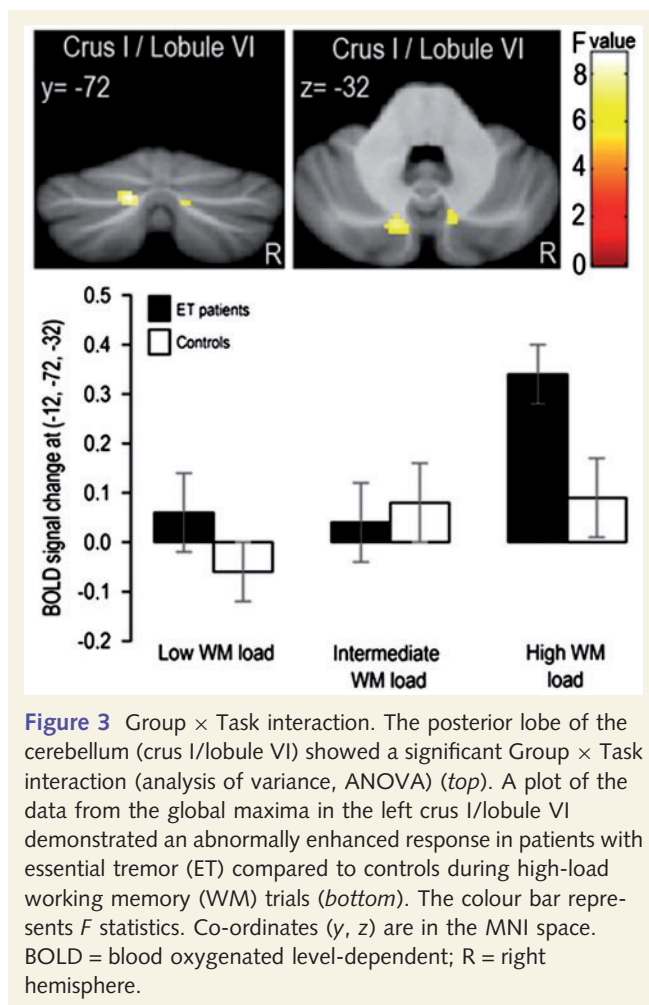
It is important to highlight that we restricted our study to patients with essential tremor with normal dopamine transporter scan, no dementia and not taking medications that alter cognitive functions and underlying brain circuits. These rigorous inclusion criteria were adopted because we aimed to explore neural correlates of verbal working memory in essential tremor in the absence of confounding effects driven by eventual parkinsonisms, global cognitive decline or pharmacological therapies, respectively.

The overactivation of posterior lobules of the cerebellum (crus I/lobule VI) in patients with essential tremor during high-load working memory trials was associated with reaction time and accuracy, which were comparable to those recorded in controls; hence, this may represent a brain compensatory mechanism that maintains the behavioural performances within a normal range. Crus I/lobule VI is involved in a number of cognitive functions including language, visuospatial skills and working memory (Schmahmann, 2004; Stoodley and Schmahmann, 2010). After a series of functional MRI experiments (Desmond and Fiez, 1998; Desmond *et al.*, 2003; Chen and Desmond, 2005), it was proposed that crus I/lobule VI supports a specific subcomponent of working memory: the articulatory loop (Baddeley, 1992). This cognitive process is thought to refresh the content of working memory via a subvocal rehearsal that prevents the decaying of memory traces (Baddeley *et al.*, 1998). Cerebellar overactivation in patients with essential tremor may therefore represent an increased effort to subvocally refresh stimuli during attentional-demanding conditions such as high-load working memory trials. Altered inner speech and rehearsal disturbances in patients with essential tremor may also depend on subclinical dysarthria, as previously demonstrated (Kronenbuerger *et al.*, 2009). However, our functional MRI paradigm did not explicitly measure overt articulatory
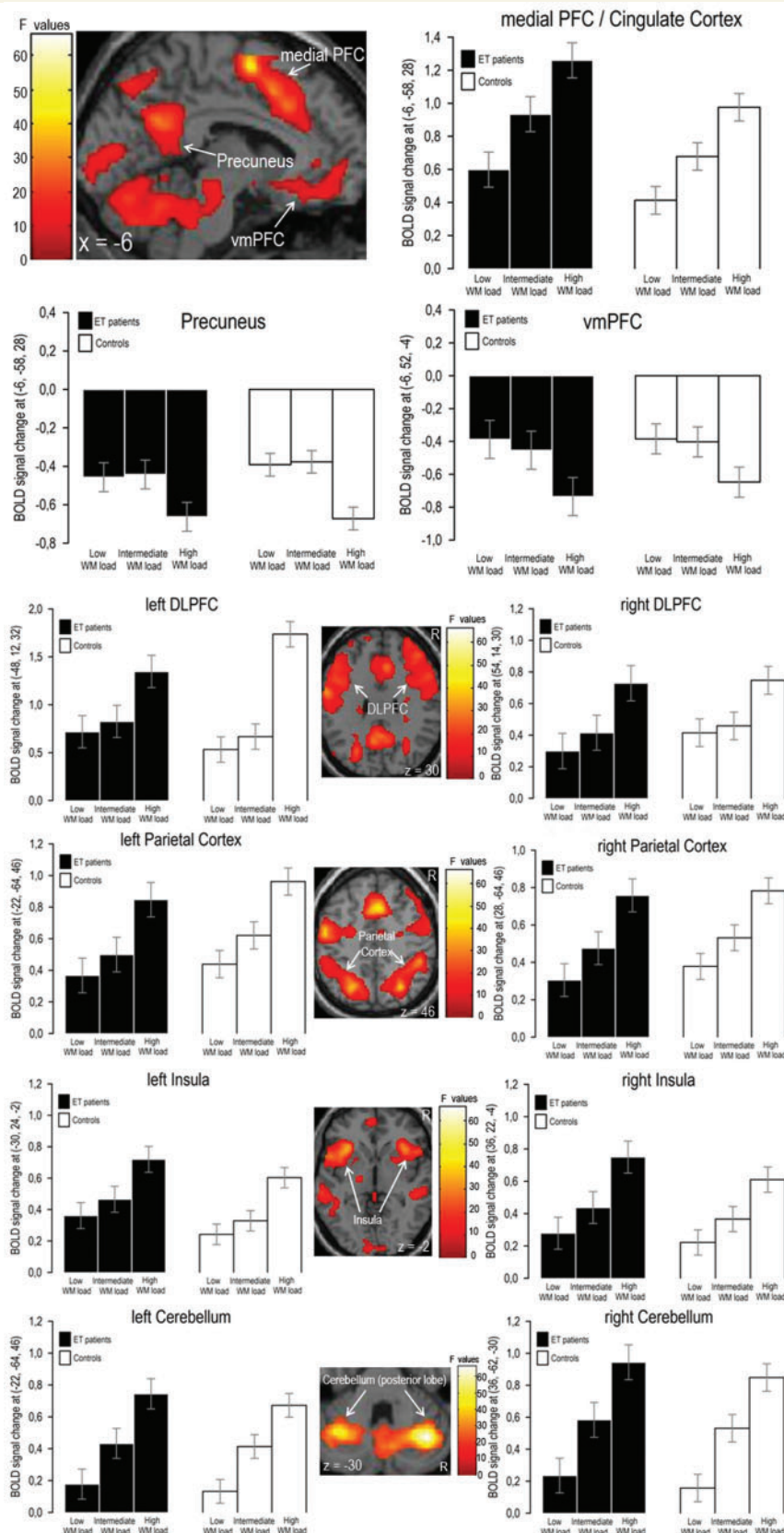
Figure 2 Main effect of the task (working memory load). Brain regions showing a main effect of the task [high-, intermediate-, low-load working memory (WM)]. The colour bar represents *F* statistics. Co-ordinates (*x*, *z*) are in the MNI space. BOLD = blood oxygenation level-dependent; DLPFC = dorsolateral-prefrontal cortex; ET = essential tremor; R = right hemisphere; vmPFC = ventromedial prefrontal cortex.

Figure 3 Group × Task interaction. The posterior lobe of the cerebellum (crus I/lobule VI) showed a significant Group × Task interaction (analysis of variance, ANOVA) (*top*). A plot of the data from the global maxima in the left crus I/lobule VI demonstrated an abnormally enhanced response in patients with essential tremor (ET) compared to controls during high-load working memory (WM) trials (*bottom*). The colour bar represents *F* statistics. Co-ordinates (*y*, *z*) are in the MNI space. BOLD = blood oxygenated level-dependent; R = right hemisphere.

Figure 4 Cerebellar activity and individual difference in cognition in patients with essential tremor. Activity in the posterior lobe of the cerebellum (lobule VI) (high- versus low-load working memory contrast) showed a positive correlation with individual scores on a measure of cognitive control (Frontal Assessment Battery scores) in patients with essential tremor (*top*). Plot of the data from the local maxima in the lobule VI (*bottom*) (r^2 value = 0.64, included to assist in the interpretation of the slope). Correlation line is shown in black and confidence intervals are shown in red. The colour bar represents *T* statistics. Co-ordinates (*y*, *z*) are in the MNI space. BOLD = blood oxygenated level-dependent.
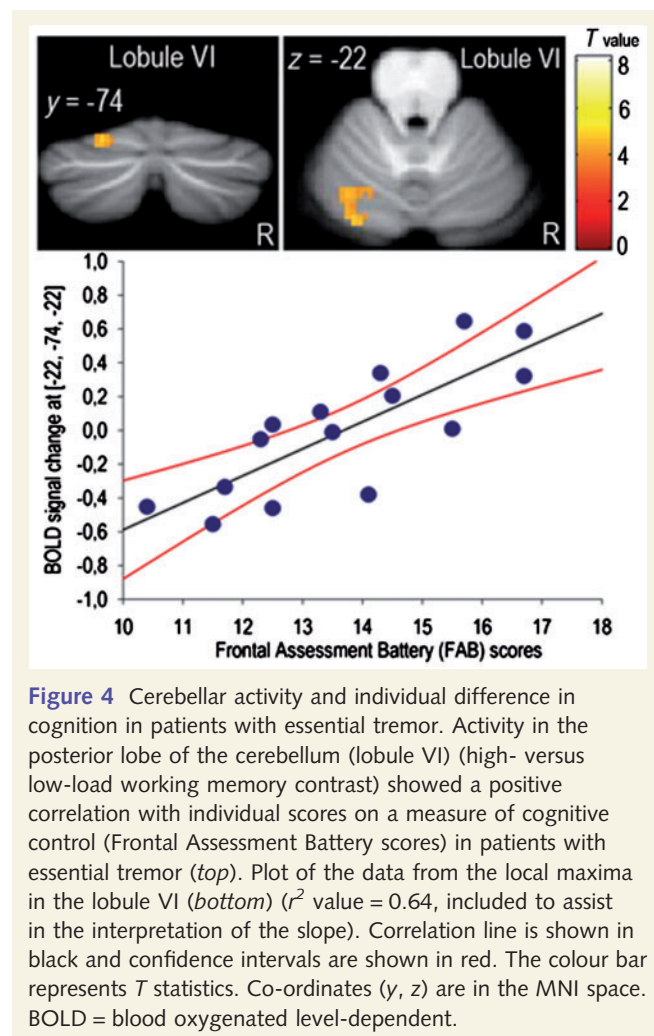
rehearsal and thus we cannot exclude that other non-linguistic processes, such as visuospatial mechanisms, may also play a role.

Similar compensatory hyperactivations of lobule VI during verbal working memory are present in individuals suffering from chronic alcoholism, a toxic condition associated with neurodegeneration of the cerebellum (Desmond *et al.*, 2003). Furthermore, we demonstrated that enhanced activation of lobule VI was associated with high cognitive control (high Frontal Assessment Battery scores) and low disease severity in patients with essential tremor (vice versa for low Frontal Assessment Battery scores and high disease severity). Although cerebellar responses discussed thus far were generally bilateral, there was a prevalence for the left rather than the right hemisphere, which is typically dominant for verbal tasks (Chen and Desmond, 2005; Durisko and Fiez, 2010). Overall, we believe that enhanced right cerebellar activation and the additional recruitment of contralateral areas may represent a key mechanism that limits the clinical expression of cognitive deficits. It is also likely that when these functional adaptations are overridden by the disease progression, local responses decrease and severe cognitive symptoms appear, although this hypothesis remains to be verified in longitudinal studies.

A critical issue regards the nature of the neurobiological mechanisms underlying abnormal cerebellar responses in patients with essential tremor. We speculate that the pathological changes associated with essential tremor (Purkinje's cells death, axonal 'torpedos', heterotopic neurons) are responsible for a dynamic reshaping/remodelling of local microcircuits that ultimately leads to altered cerebellar activations. There is also evidence that brain hyperexcitability in essential tremor may result from reduced inhibitory neurotransmission (Koller *et al.*, 1987; Mally and Stone, 1991). Other possibilities are that the overactivation represents a functional compensation for focal grey matter damage in the cerebellum (Quattrone *et al.*, 2008; Benito-Leon *et al.*, 2009; Cerasa *et al.*, 2009) or for widespread anatomical disconnections within cortical-cerebellar pathways (Shin *et al.*, 2008; Jia *et al.*, 2010; Nicoletti *et al.*, 2010). In the present study, we provide compelling evidence that disrupted functional interactions within distinct cortical-cerebellar circuits responsible for verbal working memory are an important mechanism underlying cognitive dysfunctions in essential tremor.

Of note, we found that patients with essential tremor displayed, relative to controls, disrupted functional coupling between crus I/lobule VI and the executive control circuit (dorsolateral prefrontal cortex, thalamus, inferior parietal cortex) as well as the default
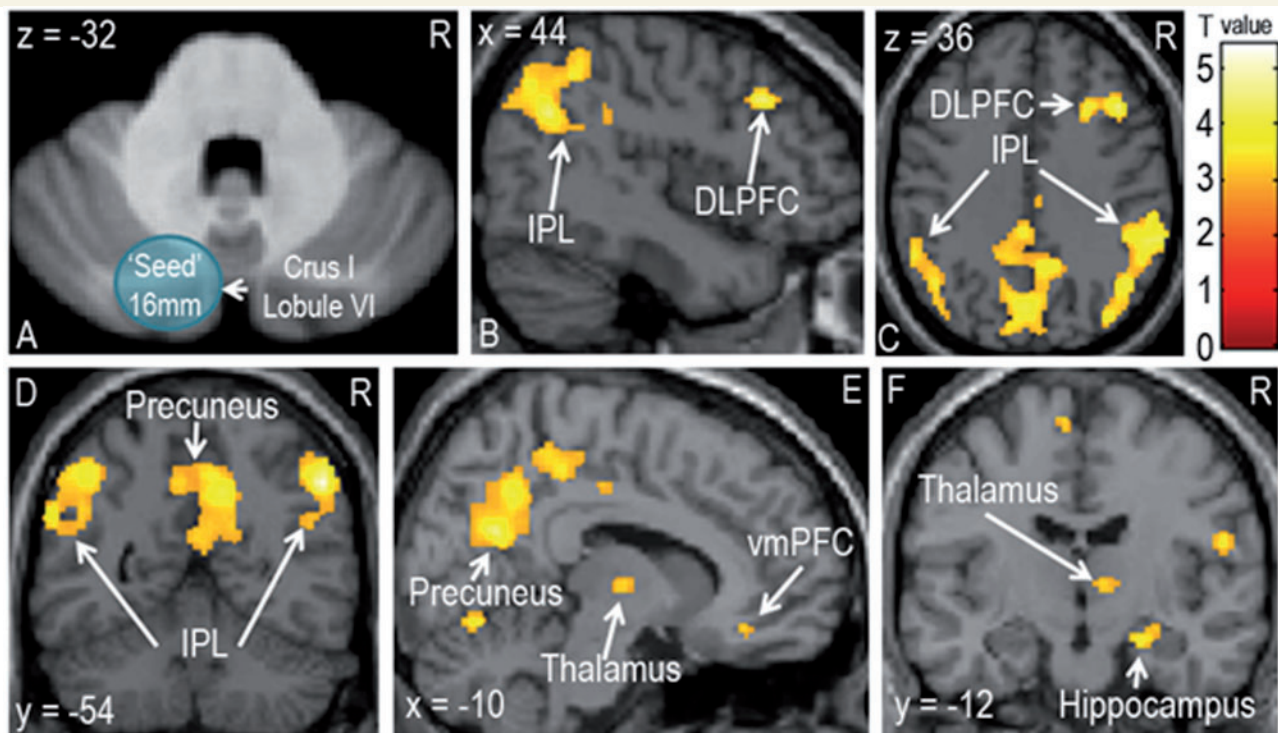
Figure 5 Cerebellar functional connectivity (Controls > patients with essential tremor). Differences in functional connectivity (psycho-physiological interaction) between the cerebellar source/seed (crus I/lobule VI) (**A**) and brain regions of the executive control circuit (inferior parietal lobe, dorsolateral prefrontal cortex, thalamus) (**B–F**) and the default mode network (precuneus; ventromedial pefrontal cortex, hippocampus) (**D–F**) when comparing controls versus patients with essential tremor for the contrast high- versus low-load working memory. The colour bar represents T statistics. Co-ordinates (x, y, z) are in the MNI space. IPL = inferior parietal lobules; DLPFC = dorsolateral prefrontal cortex; R = right hemisphere; vmPFC = ventromedial prefrontal cortex.

mode network (precuneus cortex, ventromedial prefrontal cortex, hippocampus). Histological studies have demonstrated anatomically segregated cortical-cerebellar circuits including sensory-motor and cognitive loops (Clower et al., 2001; Middleton and Strick, 2001). Particularly relevant to the present findings are the pathways linking, via relay neurons within the pons, the dorsolateral prefrontal cortex, inferior parietal lobules and anterior cingulate cortex to crus I/II and lobules VI/VII of the cerebellum (Stoodley and Schmahmann, 2010). Furthermore, recent findings demonstrated a strong intrinsic functional connectivity between crus I/lobule VI and both the executive control circuit and default mode network (Habas et al., 2009; Krienen and Buckner, 2009). Although debate exists regarding the precise function of the default mode network (Morcom and Fletcher, 2007), it has been consistently shown that during attentional demanding tasks, default mode network activity is anti-correlated to that of executive control circuit (increased activity of executive control circuit is coupled to decreased default mode network function as task difficulty increases and vice versa) (Gusnard and Raichle, 2001). In particular, it has been proposed that default mode network activity represents the insurgence of spontaneous self-referential thoughts (e.g. free recall, future planning, mind wandering) that are unrelated to task goals and that tend to worsen behavioural performances (Fox et al., 2005). In contrast, active suppression of these irrelevant thoughts via focused attention would be implemented by the executive control circuit that ultimately produces an accuracy improvement (Fox et al., 2005). Our data of reduced coupling between crus I/lobule VI and dorsolateral prefrontal cortex and increased connectivity between crus I/lobule VI and precuneus in patients with essential tremor with poor cognitive control (low Frontal Assessment Battery scores) can be viewed as a functional imbalance between executive control circuit and default mode network. It is possible that during high-load working memory trials, crus I/lobule VI facilitates executive control circuit function while disengaging default mode network (vice versa when attention is not required); this switcher role of the cerebellum would guarantee a correct optimization of cognitive resources in accordance to ongoing needs. Hence, poor cognitive control in patients with essential tremor may reflect abnormalities in switching from default mode network to executive control circuit, particularly when task demands are elevated, such as during high-load working memory trials. This interpretation is supported by evidence showing that the cerebellum plays a key regulatory role between competitive cognitive networks (Dosenbach et al., 2008). However, we acknowledge that the presence of dysfunctions in the default mode network of patients with essential tremor requires additional empirical confirmations, possibly from experiments employing different techniques from those used in the
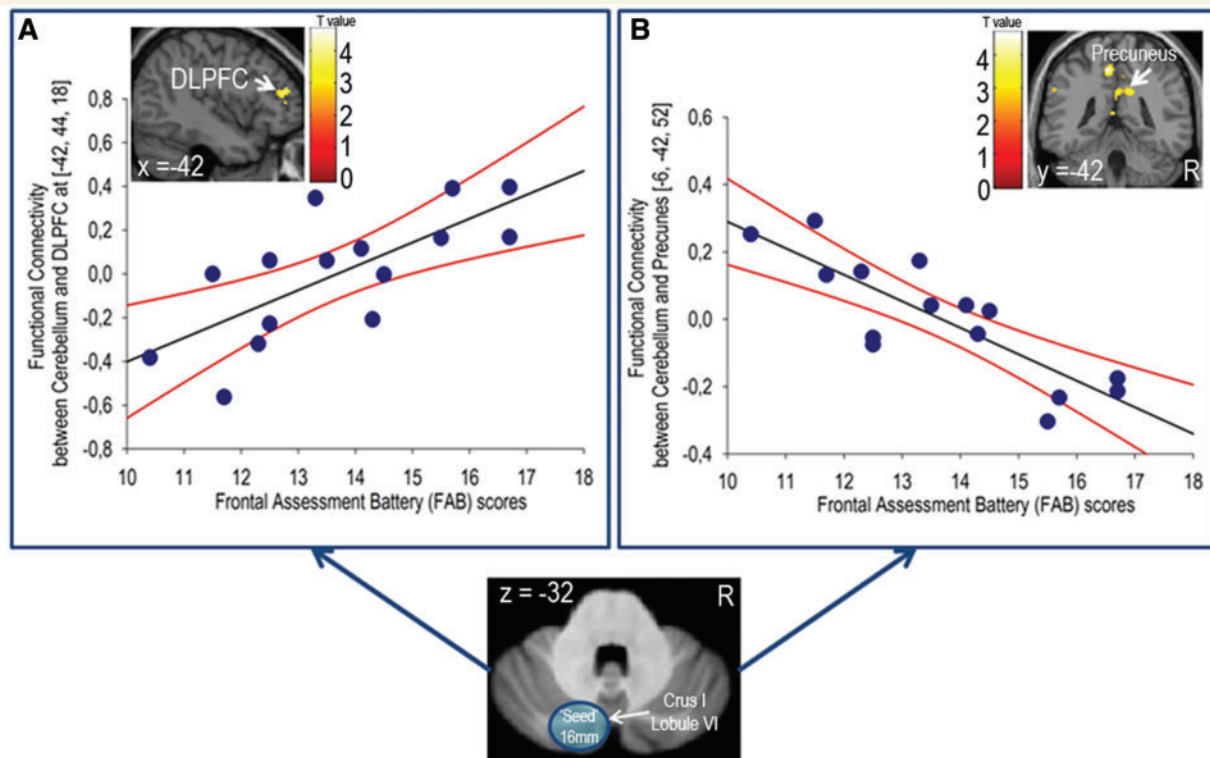
Figure 6 Cerebellar functional connectivity (individual differences in cognition in patients with essential tremor). Higher-order psycho-physiological interaction. (**A**) Individual scores in a measure of cognitive control (Frontal Assessment Battery) in patients with essential tremor are positively correlated with the connectivity between the cerebellar source/seed (*bottom*) and the dorsolateral pre-frontal cortex (r^2 value = 0.52, included to assist in the interpretation of the slope). (**B**) In contrast, Frontal Assessment Battery scores were negatively correlated with the connectivity between the source/seed and the precuneus for the contrast high- versus low-load working memory ($r^2 = -0.69$, included to assist in the interpretation of the slope). The colour bar represents *T* statistics. Co-ordinates (*x, y, z*) are in the MNI space. Correlation lines are shown in black and confidence intervals are shown in red. DLPFC = dorsolateral prefrontal cortex; ET = essential tremor; R = right hemisphere.

current study (e.g. resting state functional MRI). These methods allow a direct exploration of the default mode and other neural networks without the execution of attention-challenging tasks; hence, they would be useful tools to probe brain activity, even in those patients with essential tremor with severe cognitive impairments.

Nonetheless, our results suggest an intriguing hypothesis for future research. Diffuse abnormalities within the executive control circuit (dorsolateral prefrontal cortex; parietal lobules) and the default mode network (precuneus/retrosplenial cortex, hippocampus) are the hallmarks of Alzheimer's disease (Greicius *et al.*, 2004); hence, it could be that fundamental brain mechanisms underlying cognitive deficits in essential tremor resemble those implicated in Alzheimer's disease. Initial support for this hypothesis comes from epidemiological research showing that ~70% of patients with essential tremor who develop dementia met the criteria for probable Alzheimer's disease (Bermejo-Pareja *et al.*, 2007).

In conclusion, our findings reveal a complex picture of patho-physiological mechanisms underlying cognition in essential tremor and suggest the existence of potential similarities between essential tremor and Alzheimer's disease. Future research will confirm

whether these commonalities are consistent and whether they can be used as reliable brain markers that may efficiently guide interventions for cognitive impairments in essential tremor.

Supplementary material

Supplementary material is available at *Brain* online.

Acknowledgements

Funding

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