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Cognitive load amplifies Parkinson's tremor through excitatory network influences onto the thalamus

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Parkinson's tremor is related to cerebral activity in both the basal ganglia and a cerebello-thalamo-cortical circuit. It is a common clinical observation that tremor markedly increases during cognitive load (such as mental arithmetic), leading to serious disability. Previous research has shown that this tremor amplification is associated with reduced efficacy of dopaminergic treatment. Understanding the mechanisms of tremor amplification and its relation to catecholamines might help to better control this symptom with a targeted therapy. We reasoned that, during cognitive load, tremor amplification might result from modulatory influences onto the cerebello-thalamo-cortical circuit controlling tremor amplitude, from the ascending arousal system (bottom-up), a cognitive control network (top-down), or their combination. We have tested these hypotheses by measuring concurrent EMG and functional MRI in 33 patients with tremulous Parkinson's disease, OFF medication, during alternating periods of rest and cognitive load (mental arithmetic). Simultaneous heart rate and pupil diameter recordings indexed activity of the arousal system (which includes noradrenergic afferences). As expected, tremor amplitude correlated with activity in a cerebello-thalamo-cortical circuit; and cognitive load increased tremor amplitude, pupil diameter, heart rate, and cerebral activity in a cognitive control network distributed over fronto-parietal cortex, insula, thalamus and anterior cingulate cortex. The novel finding, obtained through network analyses, indicates that cognitive load influences tremor by increasing activity in the cerebello-thalamo-cortical circuit in two different ways: by stimulating thalamic activity, likely through the ascending arousal system (given that this modulation correlated with changes in pupil diameter), and by strengthening connectivity between the cognitive control network and the cerebello-thalamo-cortical circuit. We conclude that both the bottom-up arousal system and a top-down cognitive control network amplify tremor when a Parkinson's patient experiences cognitive load. Interventions aimed at attenuating noradrenergic activity or cognitive demands may help to reduce Parkinson's tremor.

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Abbreviations: BOLD = blood oxygen level-dependent; DCM = dynamic causal modelling; PPI = psycho-physiological interaction; VLpv = ventrolateral nucleus of thalamus, pars ventralis

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Introduction

Parkinson's disease is a neurodegenerative disorder characterized by variable combinations of bradykinesia, rigidity and a 4–6 Hz resting tremor (Postuma *et al.*, 2015). The expression of Parkinson motor symptoms is markedly influenced by emotional and cognitive states (Metz, 2007; Shine *et al.*, 2013; Nieuwhof *et al.*, 2017). Resting tremor is a prototypical example: its amplitude increases dramatically when patients experience stress or cognitive load (Marsden and Owen, 1967; Raethjen *et al.*, 2008; Zach *et al.*, 2015). In the examination room, clinicians exploit this phenomenon to make tremor more detectable, e.g. by using a serial-subtraction arithmetic task while observing the tremor. In daily life, tremor amplification can be debilitating for patients. The mechanisms linking stress and cognitive load to tremor amplification remain unclear, which prevents a targeted therapy. Building on previous work showing how basal ganglia initiate tremor episodes and a cerebello-thalamo-cortical motor loop maintains and modulates tremor amplitude (Dirkx *et al.*, 2016, 2017), here we test the hypothesis that stress and cognitive load increase tremor amplitude through the cerebello-thalamo-cortical loop (Helmich, 2018).

Previous studies indicate that the noradrenergic system may have a role in tremor amplification during stress and cognitive load (Isaias *et al.*, 2011; Helmich, 2018). Specifically, intravenous injection of adrenaline increases Parkinson's tremor (Barcroft *et al.*, 1952), and this effect can be removed using beta blockers (Marsden and Owen, 1967). Furthermore, tremor-dominant patients show less degeneration of the locus coeruleus than non-tremor patients (Paulus and Jellinger, 1991). The locus coeruleus sends noradrenergic projections to all nodes of the cerebello-thalamo-cortical circuit (Samuels and Szabadi, 2008) and especially the thalamus (Sommerauer *et al.*, 2018). In healthy individuals, activation of the locus coeruleus noradrenergic system during cognitive tasks optimizes behavioural performance (Aston-Jones and Cohen, 2005; Murphy *et al.*, 2011). The locus coeruleus noradrenergic system is also activated during psychological stress, triggering widespread cerebral activity in salience and executive networks (Hermans *et al.*, 2014; van Oort *et al.*, 2017). Thus, stress and cognitive load might increase tremor amplitude in the cerebello-thalamo-cortical circuit through bottom-up increased activity of the locus coeruleus noradrenergic system.

However, it is unlikely that noradrenergic activity is the only mechanism responsible for tremor amplification when patients experience stress or cognitive load. For instance, beta blockers inhibit the effect of (intravenously injected) adrenalin on tremor, but they do not inhibit the effect of mental arithmetic on tremor (Marsden and Owen, 1967). This raises the possibility that a cerebral control network recruited by a high cognitive load amplifies tremor through top-down interactions with the cerebello-thalamo-cortical circuit. More specifically, it has been argued that a cognitive task may act like a distractor, thereby interfering with cerebral mechanisms that inhibit tremulous activity at rest (Kaski, 2015). Alternatively, increased pathological coupling between cognitive and motor networks in Parkinson's disease may cause a spread of neural activity from one network to the other (Kim *et al.*, 2017; Nieuwhof *et al.*, 2017).

Here we investigated circuit-level mechanisms through which stress and cognitive load amplify Parkinson's tremor. Stress and cognitive load could amplify tremulous activity through noradrenergic influences onto the cerebello-thalamo-cortical tremor circuit, or through altered interactions between a cognitive control network and the cerebello-thalamo-cortical tremor circuit. We tested these two non-mutually exclusive hypotheses by recording concurrent EMG and functional MRI while 33 patients with tremulous Parkinson's disease were cognitively challenged with a mental arithmetic task. Using dynamic causal modelling (Friston *et al.*, 2003), we tested whether cognitive load amplifies tremulous activity in the cerebello-thalamo-cortical circuit directly or through the mediation of a cognitive control network. Using psycho-physiological interaction (PPI) analysis (Friston *et al.*, 1997), we tested whether these effects occur through increased excitability or disinhibition.

Materials and methods

Study population

We included 40 patients diagnosed with Parkinson's disease (according to the UK Brain Bank criteria) and a history of resting tremor. Exclusion criteria were: (i) neurological co-morbidity; (ii) signs of psychogenic tremor (e.g. entrainment or distractibility); (iii) known allergy against levodopa-benserazide or domperidone; (iv) significant cognitive impairment [Mini-Mental State Examination score <24 (Folstein *et al.*, 1975) or Frontal Assessment Battery <12 (Dubois *et al.*, 2000)]. The study was approved by the local Ethics Committee and written informed consent was collected before inclusion. We included only patients who showed a clear tremor during scanning, as evidenced by a clear 4–6 Hz peak in the EMG power spectrum. This resulted in 33 tremor-dominant Parkinson's disease patients (Table 1). Patients were tested in a practically defined OFF state [i.e. >12 h after their last dose of levodopa, >30 h after their last dose of dopaminergic agonists and >24 h after their last dose of beta blockers (Albanese *et al.*, 2001; Zach *et al.*, 2017)] and after abstention from caffeine (tea, coffee) for at least 12 h. Data collection took place at the Donders Institute (Centre for Cognitive Neuroimaging) in Nijmegen from July 2014 until February 2016.

Experimental design and behavioural parameters

During scanning, we used a block design to test for the effects of cognitive load (5×1 min rest interchanged with 5×1 min performing mental arithmetic). We chose 1-min blocks because

Table 1 Clinical characteristics

Characteristic	Mean (±SD)
Age	66 (9.7)
Male/female	22/11
Disease duration, years	3.1 (2.4)
Hoehn and Yahr	2 (1–3)
FAB	17.2 (0.9)
MMSE	29 (1.3)
LEDD	421 (276)
Levodopa usage	28/33
Dopamine agonist usage	9/33
Beta-blocker usage	4/33
MDS-UPDRS	
Total	42.0 (14.4)
Non-tremor (B + R)	
Most	11.7 (4.5)
Least	7.6 (4.0)
Axial	4.1 (2.8)
Rest tremor	
Most	4.5 (1.4)
Least	2.2 (1.7)
Constancy	3.7 (0.7)

Disease characteristics of all patients (n = 33) included for the functional MRI part are shown [Hoehn and Yahr: median, minimum and maximum scores in parentheses; other parameters: mean, standard deviation (SD) in parentheses]. Disease severity of each patient was measured using the Hoehn and Yahr stages (maximum is 5) and the MDS-UPDRS part III (maximum score is 132). Limb rigidity was calculated as the sum of MDS-UPDRS item 3 (excluding item 'Neck'), limb bradykinesia as the sum of items 4–8 and limb resting tremor as the sum of item 17 (excluding item 'Lip/Jaw') and 18. B + R = bradykinesia + rigidity; FAB = Frontal Assessment Battery; LEDD = levodopa equivalent daily dosage; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination.

we were specifically interested in the transition of tremor power between rest and cognitive load, which can be reliably captured with this timing (Raethjen *et al.*, 2008; Zach *et al.*, 2017). Specifically, patients were either presented with the words 'RUST' (Dutch for rest) or with numbers specifying a mental arithmetic task they had to perform as fast as possible ('100 – 3', '100 – 6', '100 – 7', '100 – 8', '100 – 9'; hereafter referred to as 'cognitive load'). Importantly, patients performed the task in silence, without overt motor responses, given that motor co-activation also increases tremor (Raethjen *et al.*, 2008). Patients were instructed to lie still with eyes open during rest and to perform the mental arithmetic task as fast as possible during cognitive load and to start over if they reached zero. Patients were informed that we were monitoring performance (social evaluation) by online monitoring of pupil diameter. This paradigm was based on previous data showing a clear increase in tremor power during this mental arithmetic task under social evaluation (Raethjen *et al.*, 2008; Zach *et al.*, 2017).

We simultaneously recorded three behavioural parameters during scanning: tremor (using EMG) and two proxy measures of the ascending arousal system (Murphy *et al.*, 2011; Boron and Boulpaep, 2016): pupil diameter (using continuous eye tracker recordings of the left eye) and heart rate (using a pulse oximeter on the left index finger). Details about the acquisition and analyses of these parameters can be found in the Supplementary material. We calculated the mean time course across subjects of each parameter. We also investigated the relationship between tremor and pupil diameter/heart rate in each patient, to detect a possible link between tremor and the ascending arousal system. Thus, we calculated the correlation coefficient (Pearson's R) between the time courses of tremor and pupil diameter/heart rate for each subject and subsequently tested for significant group effects using one-sample t-test (two-tailed). We did this both for the entire time course and separately for each condition (cognitive load, rest; averaged over trials; Fig. 1D). To remove transition effects from the latter analysis, we removed the first and last 3 s of each trial.

Image acquisition and functional MRI analyses

Functional MRI was performed on a 3 T MRI system (Siemens PRISMA). We used a multi-band echo planar imaging sequence (multi-band acceleration factor = 4; repetition time = 0.859 s; echo time = 34 ms; 44 axial slices; voxel size = 2.2 mm isotropic; field of view = 225 mm; scanning time ∼10 min; 700 images). The first five images were discarded. High resolution anatomical images were acquired using a magnetization-prepared rapid gradient-echo sequence (repetition time = 2.300 s; echo time = 3.03 ms; voxel size = 1.0 mm isotropic; 192 sagittal slices, field of view = 256 mm; scanning time ∼5 min).

Functional MRI images were analysed using SPM12 (http://www.fil.ion.ucl.ac.uk) and FEAT (FMRI Expert Analysis Tool) 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). First, we used ICA-AROMA (independent component analysis-based automatic removal of motion artefacts) to remove noise components in an automated, observer-independent manner (Pruim *et al.*, 2015). We performed these preprocessing steps in FSL: image registration, motion correction, non-brain removal, spatial smoothing (using a Gaussian kernel of 5 mm full-width at half-maximum) and grand-mean intensity normalization (Jenkinson and Smith, 2001). All components were visually checked and if necessary corrected. Next, output images from ICA-AROMA (realigned and in native space) were further preprocessed in SPM12: (i) co-registered to structural MRI image; (ii) normalized to MNI (Montreal Neurological Institute) space; and (iii) spatially smoothed using a 6-mm Gaussian kernel (resulting in a net smoothing kernel of 7.8 mm). Structural images were segmented and normalized using a unified segmentation approach (Ashburner and Friston, 2005). None of the patients showed excessive movement during scanning, defined as scan-to-scan movement exceeding the voxel size (2.2 mm). Across the group, the Euclidean distance travelled by the head from the first to the last scan was 1.3 ± 0.2 mm [average ± standard error of the mean (SEM)] and the mean-per-scan movement (Euclidean distance) was 0.1 ± 0.009 mm.

After preprocessing, we performed a multiple regression analysis at the first level for each subject to test for effects of cognitive load, tremor, and their interaction. We used a general linear model (GLM) including regressors describing tremor amplitude/change. To filter any residual movement-related artefacts (e.g. due to tremor), we also added two regressors of no interest [average signal across the whole brain and bilateral ventricles to correct for non-neural noise (Power *et al.*, 2014)]. To compare tremor-related effects between rest and cognitive load, we separately modelled both conditions on a scan-by-scan basis (with a duration of one repetition time), and added tremor amplitude (EMG-amp) and its first temporal derivative (EMG-change) as a parametric modulation for each scan. This resulted in six

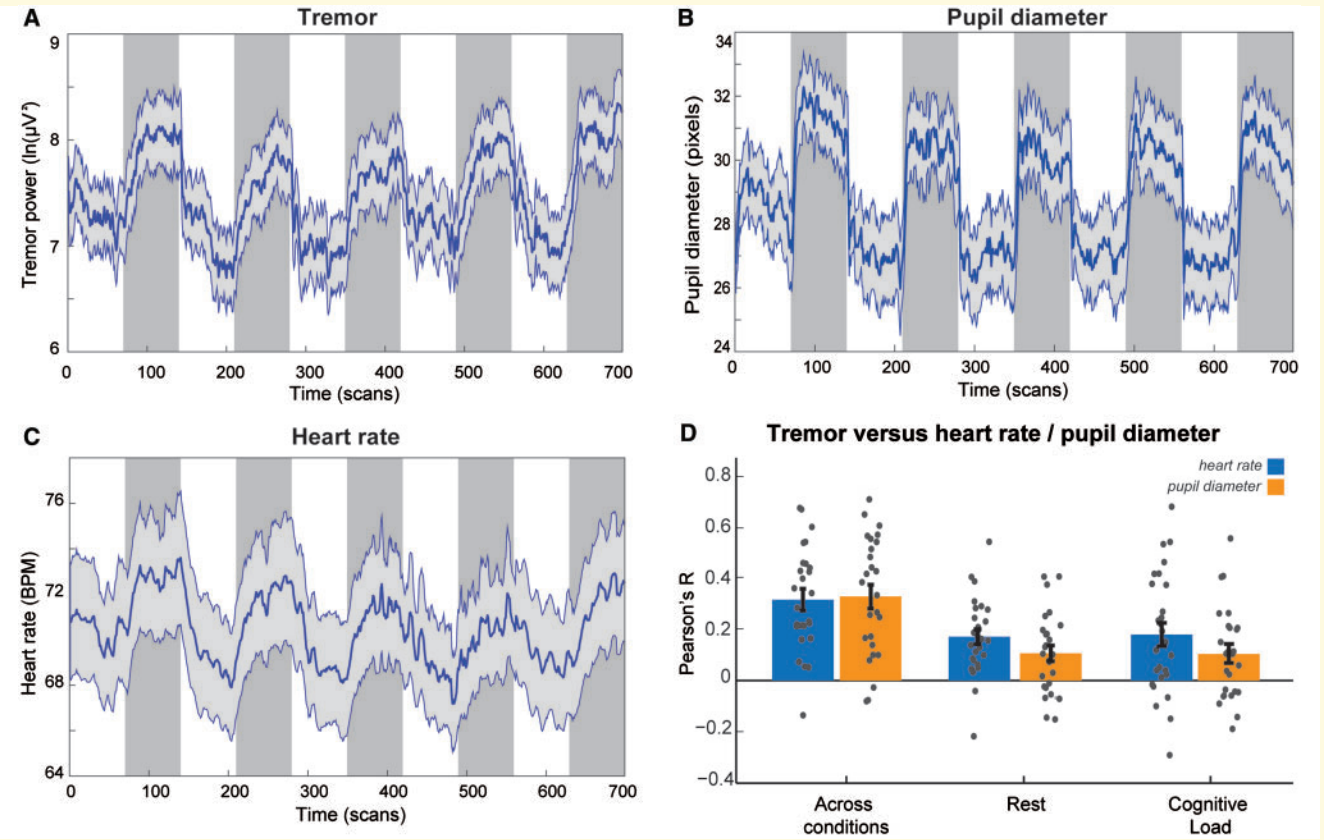

Figure 1 Behavioural effects of cognitive load. Effects of cognitive load on behavioural parameters showing an increase during cognitive load (grey blocks) of (**A**) tremor amplitude (**B**) pupil diameter and (**C**) heart rate. (**D**) Tremor amplitude is significantly correlated with pupil diameter and heart rate. BPM = beats per minute.

regressors: rest, rest-EMG-amp, rest-EMG-change, cognitive load, cognitive load-EMG-amp, and cognitive load-EMG-change. For four patients accelerometry signal was used instead of EMG due to noisy recordings. This design allowed us to identify and distinguish between cerebral activity related to performance of the cognitive task (cognitive load > rest), tremor amplitude-related activity (averaged effects of rest-EMG-amp and cognitive load-EMG-amp), tremor change-related activity (averaged effects of rest-EMG-change and cognitive load-EMG-change), and tremor-related effects specific for cognitive load (cognitive load-EMG-amp > rest-EMG-amp; cognitive load-EMG-change > rest-EMG-change). All parameters were estimated using maximum likelihood estimation. Next, first-level contrasts entered a second-level analysis using one-sample *t*-tests.

For all our second-level analyses, we performed a whole brain search using a threshold of $P < 0.05$ familywise error (FWE) corrected, either at the voxel level (where we expected a high localization power, i.e. cognitive load > rest) or at the cluster level (to optimize sensitivity for contrasts where we expect a smaller effect size) with a cluster-forming threshold of $P < 0.001$ (Eklund *et al.*, 2016). We used the SPM Anatomy Toolbox (Eickhoff *et al.*, 2005) for anatomical localization. Besides whole-brain analyses, we also performed dedicated region of interest analyses in brain regions where we previously showed tremor-related activity: contralateral motor cortex [Brodmann area (BA) 4/6, 3712 mm^3 (Helmich *et al.*, 2011)], contralateral ventrolateral nucleus of thalamus, pars ventralis [VLpv (Morel *et al.*, 1997), 768 mm^3], ipsilateral cerebellum [lobule V/VI, 1416 mm^3 (Helmich *et al.*, 2011)]; and contralateral internal globus pallidus (GPi, 664 mm^3) and external globus pallidus (GPe, 2256 mm^3), from the Basal Ganglia Human Area Template toolbox (Prodoehl *et al.*, 2008). Region of interest analyses were performed at the voxel level, FWE-corrected for multiple comparisons.

Dynamic causal modelling

Dynamic causal modelling (DCM) is a Bayesian method of inference where one defines one or more cerebral model(s) based on predefined hypotheses to test for causal influences that one neural system exerts over the other (Friston *et al.*, 2003). Specifically, one defines a cerebral model by including brain regions that can be influenced by (i) fixed connections between included nodes (DCM.A); (ii) modulation of these fixed connections by exogenous inputs (DCM.B); and (iii) exogenous inputs that drive network activity (DCM.C). Subsequently, these parameters are estimated using a forward model such that the predicted blood oxygen level-dependent (BOLD) response provides an accurate but parsimonious explanation for the observed BOLD response.

In previous work, we used DCM to identify a tremor network where the basal ganglia triggered spontaneous tremor episodes and the cerebello-thalamo-cortical circuit produced and modulated tremor amplitude (Dirkx *et al.*, 2016, 2017). Here we aimed to identify the mechanism by which cognitive load (DCM.C) drives tremulous activity in the cerebello-thalamo-cortical circuit. We constructed a model space that would test our two hypotheses: (i) during cognitive load a direct (possibly noradrenergic) effect drives the cerebello-thalamo-cortical circuit and the cognitive network in parallel; and (ii) cognitive load activates a cognitive network which interacts with the cerebello-thalamo-cortical network. We tested these hypotheses using a model with four regions of interest: three regions specifying the cerebello-thalamo-cortical circuit (see above) and one region representing the cognitive control network activated during cognitive load episodes (first eigenvariate BOLD response from all regions activated during cognitive load > rest with a cluster forming threshold of $P < 0.001$ uncorrected) (Hyett *et al.*, 2015; Tsvetanov *et al.*, 2016). Furthermore, we constructed models testing if and how the cognitive control network and cerebello-thalamo-cortical circuit interact with each other (by changing connectivity parameters DCM.A). This resulted in 31 models, of which we defined eight model families (Penny *et al.*, 2010) that shared a unique connectivity fingerprint. We used deterministic DCM12.5 for all our analyses.

Next, we performed a random-effects Bayesian model selection to determine which model family most likely generated the observed BOLD responses. Bayesian model averaging was used to calculate mean parameters of the winning model family considering the relative model evidence. We then used one sample *t*-tests on each DCM.C parameter to test whether they significantly contributed as a driving input. Furthermore, we performed a one-way ANOVA with *post hoc* multiple comparisons (Tukey's least significant difference) to test whether the input parameters differed from each other. Finally, to test the hypothesis that the driving input (cognitive load) represents (in part) activity of the ascending arousal system [including noradrenergic afferences (Murphy *et al.*, 2011)] we performed a correlation analysis (Pearson's two-tailed) between the estimated DCM.C and relative increase in pupil diameter (cognitive load minus rest). Note that we chose to use *post hoc* tests to determine the ascending arousal aetiology of the network activity's driving input instead of defining the driving input as an ascending arousal proxy measure (such as pupil diameter) up front for several reasons. First, use of a basic condition regressor as DCM.C is in line with the classic DCM approach (Friston *et al.*, 2003). Second, this approach allowed for the possibility that alternative neural systems contribute to network activity during cognitive load, which seems physiologically more plausible. Third, we could include all patients, whereas an approach using pupil diameter would have resulted in exclusion of seven patients because of noisy data recordings (Supplementary material).

Psycho-physiological interaction

We tested whether functional connectivity between the cognitive control network and the cerebello-thalamo-cortical circuit decreased or increased as a function of cognitive load by performing a PPI analysis (Friston *et al.*, 1997). We entered the BOLD time course of the cognitive control network (first eigenvariate, 'Y'), the task regressor (cognitive load > rest, 'P') and their interaction (PPI; Fig. 4A) to a first level analysis, together with nuisance regressors (whole brain and lateral ventricle signal). PPI contrast images were brought to a second level analysis, with laterality of tremor as covariate. We tested for positive and negative effects on the cerebello-thalamo-cortical circuit (see above).

Supplementary analyses

Details on the acquisition and analysis of behavioural parameters during scanning can be found in the Supplementary material. To investigate the cerebral effects related to fluctuations in pupil diameter, we performed a supplementary analysis where we extended the GLM with pupil diameter as an additional parametric modulatory effect. For this, we only included the 26 patients who had a pupil diameter regressor of sufficient quality (see above). To rule out that changes in pupil diameter were driven by luminance, we compared the average pixel intensity per condition trial with pupil diameter.

To rule out that chronic usage of beta-blockers influenced our results, we reanalysed our main findings while excluding four patients who used beta-blockers.

Data availability

All derived and anonymized individual data are available at the Donders Repository (http://hdl.handle.net/11633/aac2o4pp). Statistical maps of second level analyses are also available at NeuroVault (https://identifiers.org/neurovault.collection: 6269).

Results

Behavioural effects of cognitive load on tremor, pupil diameter, and heart rate

Cognitive load significantly increased tremor amplitude [accelerometry-based power, log transformed: rest: 7.2 ± 0.3; cognitive load: 7.8 ± 0.3 (mean ± SEM); $t(32) = 5.8$, $P < 0.001$], pupil diameter [pixels: rest: 27.9 ± 1.2; cognitive load: 30.8 ± 5.6; $t(25) = 9.2$, $P < 0.001$] and heart rate [beats per minute: rest: 69.6 ± 2.4; cognitive load: 71.3 ± 2.5; $t(26) = 6.9$, $P < 0.001$; Fig. 1]. Furthermore, pupil diameter and heart rate significantly correlated with tremor amplitude across both conditions (which captures the transitions between conditions), as well as separately for rest and cognitive load (which captures the dynamics within each condition; Fig. 1D), although only a small portion of the variance (R^2 = 10–11%) was accounted for. These results suggest that (in part) similar mechanisms may be involved in the observed changes of tremor, heart rate and pupil diameter during cognitive load.

Cerebral effects of cognitive load and tremor

We distinguished between three different patterns of brain activity related to cognitive load, tremor, and their interaction. First, the cognitive task was associated with increased brain activity in a cognitive control network, which included

the bilateral anterior cingulate cortex, insula, thalamus, posterior parietal cortex, frontal eye fields, and dorsolateral prefrontal cortex (Fig. 2A and Table 2). For anatomical details, see Table 2. Second, tremor amplitude was associated with brain activity in the cerebello-thalamo-cortical circuit (across rest and cognitive load; Fig. 2B and Table 2), replicating previous results (Helmich *et al.*, 2011; Dirkx *et al.*, 2016, 2017). We did not find tremor-change activity in the basal ganglia, as shown before during rest (Helmich *et al.*, 2011; Dirkx *et al.*, 2017). Third, we observed differential tremor-related activity during cognitive load versus rest in the contralateral secondary somatosensory cortex, contralateral superior parietal cortex, and ipsilateral motor cortex (Fig. 2C and Table 2). Furthermore, the rapid increase of tremor at the beginning of cognitive blocks (tremor-change, cognitive load > rest) was associated with tremor-related activity in the thalamus (VLpv; Fig. 2C and Table 2). The same contrast also showed activity in the superior parietal cortex, but *post hoc* analyses showed that this result was driven by a negative correlation with tremor change during rest (and therefore we did not consider this finding further).

Dynamic causal modelling

A Bayesian model selection of eight model families revealed that models with bidirectional connections between the cognitive network and all nodes of the cerebello-thalamo-cortical circuit were significantly more likely (i.e. >99%) than models with fewer connections between the circuits or no connections at all (expected posterior = 0.57; exceedance probability = 0.99; Fig. 3A). Bayesian model averaging revealed that cognitive load drives network activity (i.e. DCM.C) by stimulating the cognitive control network [$t(32) = 16.7$, $P < 0.001$] and the VLpv [$t(32) = 2.9$, $P = 0.007$] but not the motor cortex [$t(32) = -0.6$, $P = 0.6$] or cerebellum [$t(32) = -0.3$, $P = 0.80$; Fig. 3C]. Further testing confirmed that the effect was specific for the VLpv [$F(2,96) = 3.8$, $P = 0.03$; VLpv versus cerebellum: $P = 0.04$; VLpv versus motor cortex: $P = 0.01$; cerebellum versus motor cortex: $P = 0.6$]. Finally, the averaged driving input of cognitive load (DCM.C) significantly correlated with cognitive load-evoked increases in pupil diameter (Fig. 3D). These results suggest that the ascending arousal system is (at least in part) responsible for tremor-related network activity during cognitive load.

Psycho-physiological interaction

The PPI analysis revealed a significant interaction (cognitive task × cognitive network activity) in the VLpv bilaterally (Table 2 and Fig. 4). This indicates increased functional connectivity between the cognitive control network and the thalamus during periods of cognitive load. This counters the hypothesis that cognitive load distracts inhibitory influences onto the VLpv (i.e. disinhibition) in which case one would expect a decrease in connectivity between circuits. Instead, it suggests that the cognitive control network stimulates the VLpv during episodes of cognitive load.

Supplementary analyses

Fluctuations in pupil diameter (across conditions) significantly correlated with cerebral activity in nine brain regions that largely overlapped with the cognitive control network. Given that fluctuations in pupil diameter are a reliable proxy measure for arousal or locus coeruleus activity (Gilzenrat *et al.*, 2010; Murphy *et al.*, 2011, 2014; Nassar *et al.*, 2012; Eldar *et al.*, 2013), this suggests that the ascending arousal system (including noradrenergic afferents) was activated during our cognitive task. We ruled out that changes in pupil dilation were explained by small differences in luminance between conditions, as there was no relationship between pupil dilation and the average pixel intensity per trial.

Apart from some minor details, we replicated our main results while excluding four patients who used beta-blockers, confirming that chronic usage did not influence our results.

Discussion

We investigated the cerebral mechanisms underlying tremor amplification in patients with Parkinson's disease during cognitive load. There are three main findings. First, cognitive load was associated with increased tremor, larger pupil diameter, faster heart rate and increased cerebral activity in a cognitive control network consisting of fronto-parietal cortex, insula, thalamus and anterior cingulate cortex. Second, while we observed tremor amplitude-related activity in the cerebello-thalamo-cortical network across conditions (Helmich *et al.*, 2011; Dirkx *et al.*, 2016), cognitive load enhanced tremor amplitude-related activity in the secondary somatosensory cortex, superior parietal cortex and ipsilateral motor cortex, as well as tremor-change related activity in the contralateral VLpv. Third, and most importantly, network analyses showed two different ways by which cognitive load modulated the cerebello-thalamo-cortical tremor circuit: directly by stimulating tremor-related processing at the level of the VLpv; and indirectly by strengthening connectivity between a cognitive control network and the cerebello-thalamo-cortical circuit. Given that the effect of cognitive load on the VLpv correlated with load-related changes in pupil diameter, we argue that this effect involves ascending arousal systems, likely the noradrenergic system. Taken together, these findings suggest that cognitive load amplifies Parkinson's tremor in two ways: both by bottom-up noradrenergic influences onto the thalamus and by top-down cognitive influences onto the thalamus, cerebellum, and motor cortex.

Cognitive load increases tremor via the ascending arousal system

The data suggest that cognitive load is associated with increased arousal, and that the ascending arousal system may drive tremor amplification during cognitive load. Arousal is controlled by the neuromodulatory systems of the brainstem, which have widespread projections to several cortical and subcortical brain regions where they tune neuronal

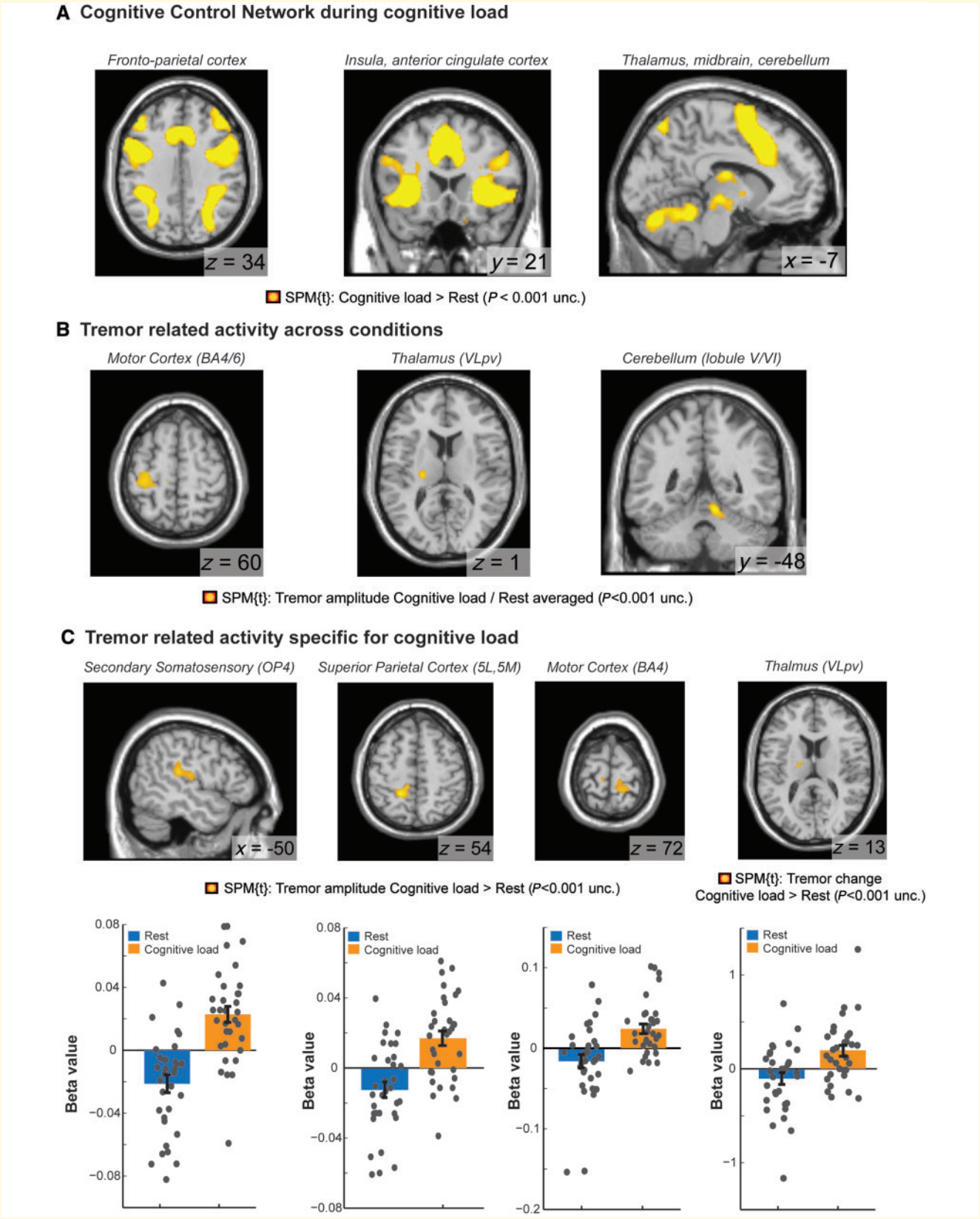

Figure 2 Cerebral (tremor-related) activity during cognitive load and rest. Cerebral activity patterns measured by functional MRI showing (**A**) the recruitment of a cognitive control network during cognitive load > rest, (**B**) tremor amplitude-related activity in a cerebello-thalamo-cortical circuit across conditions, and (**C**) increased tremor amplitude-related activity in the contralateral secondary somatosensory cortex, superior parietal cortex and ipsilateral motor cortex and increased tremor change related activity in the thalamus during cognitive load > rest. BA = Brodmann area; OP4 = opercular cortex 4.

Table 2 Cerebral (tremor-related) activity

	Voxel level inference					
Contrast	**Anatomical label**	**Anatomical location**	**Hemisphere (wrt tremor)**	**MNI (*x*, *y*, *z*)**	***T***	***P*(FWE corr.)**
Cognitive load > rest	dACC	Superior medial gyrus	Medial	4, 20, 44	17.0	<0.001
		Medial cingulate cortex		2, 14, 46	16.0	<0.001
	AI	Insula	Bilateral	–32, 22, –4	11.9	<0.001
				34, 26, –2	14.2	<0.001
	IPS	hIP3	Bilateral	–40, –48, 44	12.9	<0.001
				36, –48, 42	9.7	<0.001
	SPC	7A	Bilateral	–26, –64, 58	8.0	<0.001
				28, –76, 59	6.0	<0.001
	FEF	Superior frontal gyrus	Bilateral	–24, 2, 61	10.4	<0.001
				28, –2, 59	10.8	<0.001
	dlPFC		Bilateral	–44, 32, 30	8.3	<0.001
				46, 34, 24	9.3	<0.001
	MT	Inferior temporal gyrus	Bilateral	–54, –54, –18	13.5	<0.001
				62, –42, –22	7.4	<0.001
	CBLM	Lobule VI:				
		Hemisphere	Bilateral	32, –64, –26	11.4	<0.001
				–30, –64, –28	10.4	<0.001
		Vermis	Medial	–2, –60, –26	10.0	<0.001
	VLpv	VLpv (Morel atlas)	Bilateral	–12, –14, 6	6.8	<0.001
				16, –14, 4	5.2	<0.001
Tremor amplitude (cognitive load / rest averaged)	MC	BA4 (60%) BA6 (26%)	Contralateral	±30, –20, 54	4.8	0.002
	VLpv	VLpv (Morel Atlas)	Contralateral	±20, –18, 10	3.3	0.025
	CBLM	Lobule V (39%) Lobule VI (49%)	Ipsilateral	±12, –50, –18	4.3	0.003
Tremor change (cognitive load > rest)	VLpv	VLpv (Morel Atlas)	Contra-lateral	±16, –12, 10	3.2	0.033
PPI (cognitive load × cognitive control network)	VLpv	VLpv (Morel Atlas)	Bilateral	–12, –16, 8	3.5	0.016
				18, –18, 8	3.7	0.011

	Cluster level inference (whole brain search)					
Contrast	**Anatomical label**	**Anatomical location**	**Hemisphere (wrt tremor)**	**Cluster size (voxels)**	**Local peak (MNI *x*, *y*, *z*)**	***P*(FWE corr.)**
Tremor amplitude (cognitive load > rest)	S2	OP1 (24%) OP3 (13%) Ig2 (5%)	Contralateral	576	±46, –18, 16	<0.001
	SPC	5M (49%) 5L (8%) BA3a (5%)	Contralateral	192	±18, –44, 54	0.017
	MC	BA4a (42%) 5L (15%) BA3b (7%)	Ipsilateral	228	±12, –26, 66	0.007
Tremor change (cognitive load > rest)	SPC	7A (42%) 7PC (19%) hIP3 (15%) 5L (11%)	Ipsilateral	616	±18, –66, 60	<0.001
	SPC	7A (87%) 7P (9%)	Contralateral	244	±14, –70, 56	0.003
	SPC	7PC (44%) BA2 (24%) hIP3 (13%) 7A (9%)	Contralateral	324	±40, –50, 58	<0.001

Table showing the results of one-sample *t*-tests on functional MRI contrasts specifying general effects of cognitive load (cognitive load > rest), tremor amplitude-related activity across conditions and for cognitive load > rest, tremor change-related activity for cognitive load > rest and the results of the PPI (cognitive load × cognitive control network). Both statistical methods (at cluster and voxel level) are displayed. At the voxel level, both whole-brain corrected (for cognitive load > rest) as well as region of interest analyses have been used (for areas related to tremor). The anatomical location is determined using the Anatomy Toolbox (Eickhoff *et al.*, 2005). Percentages in parentheses behind each anatomical location correspond to percentage of tremor-related cluster that overlaps with the specified anatomical cluster. AI = anterior insula; BA = Brodmann area; CBLM = cerebellum; dACC = dorsal anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; Ig = insula lobe granula areas; IPS = infra parietal sulcus; MC = motor cortex; MT = medial temporal cortex; OP4 = operculum; pars ventralis; SPC = superior parietal cortex; wrt = with respect to.

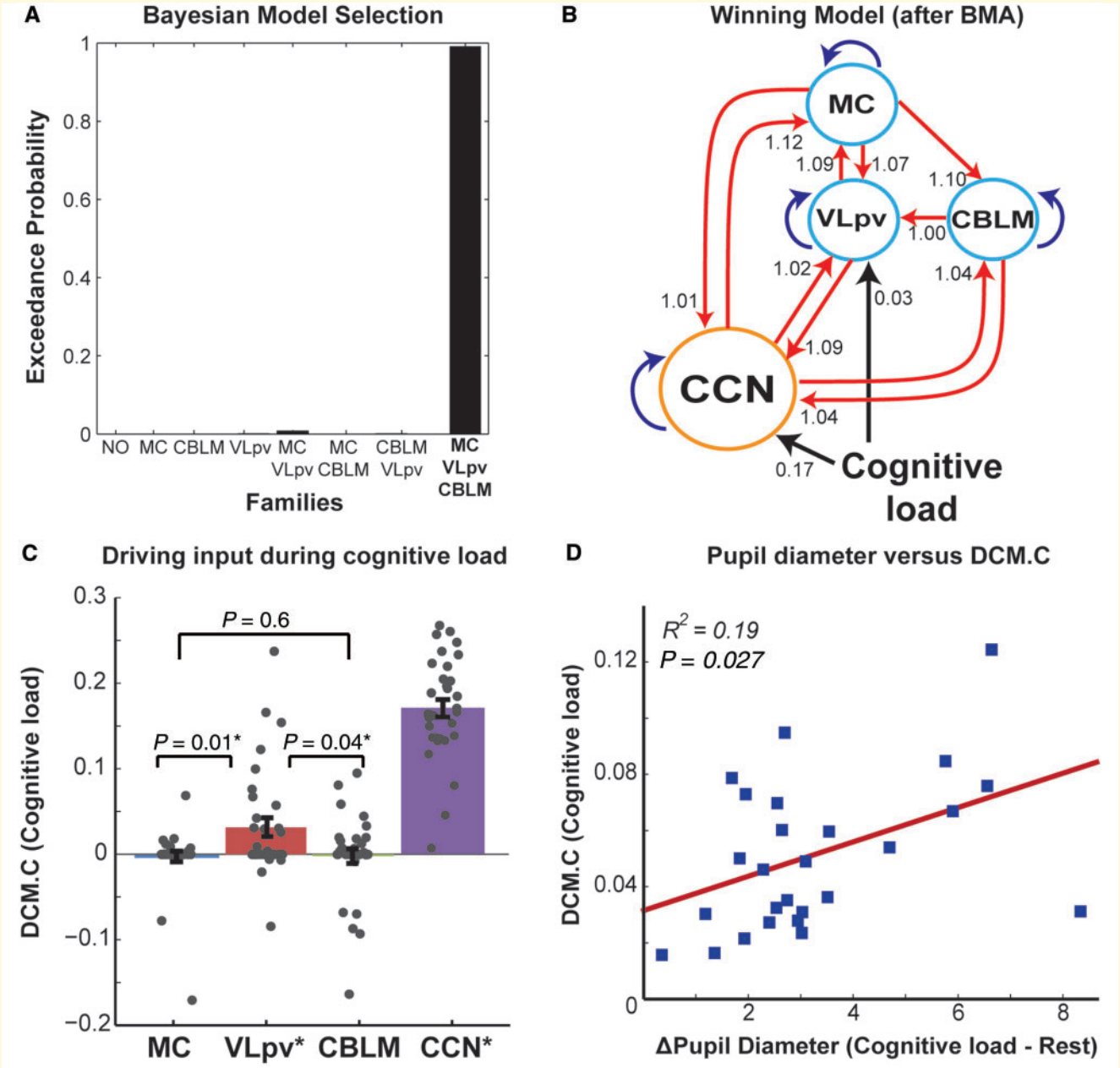

Figure 3 Dynamic causal modelling. (**A**) Bayesian Model Selection of eight model families showing that the family where the cognitive control network (CCN) has bidirectional connections with all nodes of the cerebello-thalamo-cortical circuit is significantly the strongest. (**B**) Graphical representation of the winning model and its parameters after Bayesian Model Averaging (BMA). The cerebello-thalamo-cortical circuit is indicated with blue circles, the cognitive control network with an orange one. (**C**) Comparison of the driving input during cognitive load (DCM.C) shows that there is a significant stimulating effect only on the VLpv and cognitive control network. (**D**) The averaged driving input during cognitive load (DCM.C) predicts the task-evoked increase in pupil diameter. CBLM = cerebellum; MC = motor cortex. *Significant.

parameters that govern their activity. The locus coeruleus noradrenergic system is a key component of the ascending arousal system, which operates at a timescale (seconds) that fits the observed tremor modulation (Fig. 1). Although we do not have direct measurements of noradrenergic activity, we report strong associations between several key findings and changes in pupil diameter, a clear marker of activity of the locus coeruleus noradrenergic system (Aston-Jones and Cohen, 2005; Gilzenrat *et al.*, 2010; Murphy *et al.*, 2011; Nassar *et al.*, 2012; Eldar *et al.*, 2013). Specifically, previous research has shown that pupil diameter correlates with direct locus coeruleus recordings in monkeys (Rajkowski *et al.*, 1994) and with locus coeruleus BOLD activity in humans (Murphy *et al.*, 2014). Furthermore, human behavioural

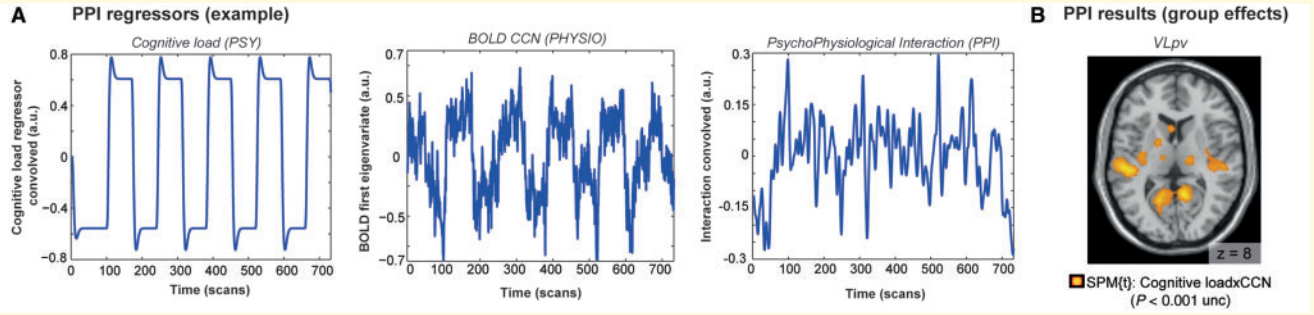

Figure 4 Psycho-physiological interaction. (**A**) Representative example of the regressors used for the PPI analyses including the convolved psychological regressor (cognitive load; *left* subplot), physiological regressor (BOLD first eigenvariate of the cognitive control network; *middle* subplot) and their interaction (calculated as the unconvolved psychological × unconvolved physiological regressor with subsequent haemodynamic convolution; *right* subplot). (**B**) Group results revealed a significant interaction (cognitive task × cognitive network activity) in the VLpv bilaterally. a.u. = arbitrary units; CCN = cognitive control network.

experiments show that fluctuations in pupil diameter predict behavioural effects related to locus coeruleus function (Gilzenrat *et al.*, 2010; Jepma and Nieuwenhuis, 2011; Murphy *et al.*, 2011), and phasic locus coeruleus firing optimizes behavioural performance during cognitive tasks (Aston-Jones and Cohen, 2005). In our own data, cognitive load in the form of a mental arithmetic task increased pupil diameter as well as brain activity in a cognitive control network, and individual variations in pupil diameter were correlated with activity in a salience network. The role of the locus coeruleus noradrenergic system in the mental arithmetic task is further supported by task-related increases in heart rate: although other neurotransmitters, such as the cholinergic system, can also influence pupil diameter (Sarter *et al.*, 2006; Reimer *et al.*, 2016), heart rate is specifically controlled by the (nor)adrenergic system (Boron and Boulpaep, 2016).

Crucially, fluctuations in pupil diameter and heart rate, as evoked by the mental arithmetic task, were correlated with fluctuations in tremor amplitude (Fig. 1D). Furthermore, the excitatory effect of cognitive load on tremor-related processing in the thalamus was correlated with inter-individual differences in pupil dilation during cognitive load (Fig. 3D). These data suggest that, in addition to dopaminergic (Dirkx *et al.*, 2017) and serotonergic influences (Pasquini *et al.*, 2018), the noradrenergic system may play a role in driving Parkinson's tremor (Isaias *et al.*, 2011). Our data indicate that the ascending arousal system does this by modulating tremor-related activity in the VLpv. This fits with previous studies showing that the locus coeruleus sends massive projections to the thalamus, where both excitatory α1-adrenoceptors and β-adrenoceptors are present (McCormick *et al.*, 1991; Samuels and Szabadi, 2008). Noradrenaline promotes a single spike firing mode of activity in the thalamus, which is associated with high excitability during periods of attentiveness and cognition (McCormick *et al.*, 1991). Interestingly, during periods of sleep—where locus coeruleus inactivity leads to thalamic burst-firing and low excitability (McCormick *et al.*, 1991)—tremor may even completely disappear (Askenasy and Yahr, 1990). However, as already put forward by others, there are clear indications that cognitive load may also amplify tremor through other mechanisms than the ascending arousal system: while beta-blockers could abolish the effect of intravenous adrenalin on tremor, it did not alter the effect of mental arithmetic on tremor in a small sample of eight patients (Marsden and Owen, 1967). As outlined below, our data indeed suggest the presence of a second, top-down cognitive mechanism.

Cognitive load increases tremor by recruiting a cognitive control network

Patients showed increased cerebral activity in a distributed cognitive network involved in attention (Fox *et al.*, 2006) and problem solving (Menon, 2011) during the mental arithmetic task used here. Mental arithmetic is an element of many stress paradigms (Pruessner *et al.*, 2008) and accordingly, large parts of this network have been implicated in attentional and sensory orienting during psychological stress (Hermans *et al.*, 2011; van Oort *et al.*, 2017). While the exact functional architecture of the cognitive network has attracted considerable attention, here we were mainly interested in understanding how that network influenced tremor-related activity in the cerebello-thalamo-cortical circuit. Our data reveal two potential mechanisms.

First, we observed increased activity in the thalamus (VLpv), which was associated with the change in tremor amplitude at the beginning of cognitive load blocks. This finding fits with the specific increase in (possibly noradrenergic) input onto the thalamus outlined above, showing that the thalamus is a key target for tremor amplification during cognitive load. Furthermore, there were three regions with increased tremor amplitude-related activity during mental arithmetic: contralateral secondary somatosensory cortex (SII), superior parietal cortex (SPC) and ipsilateral motor cortex. Both SII and SPC have been implicated in processing

afferent tremor-related input (Timmermann *et al.*, 2003; Pollok *et al.*, 2009; Helmich *et al.*, 2012). This suggests that activity in these areas may reflect increased afferent signalling as a result of tremor amplification during cognitive load (Hurtado *et al.*, 2000). The increased afferent input has been suggested to stabilize the tremor rhythm within the cerebello-thalamo-cortical circuit (Volkmann *et al.*, 1996), and there is empirical evidence that reducing tremor-related afferent input can reduce tremor amplitude (Helmich, 2018). Thus, cognitive load may produce a vicious circle where tremulous activity in the thalamus is amplified and stabilized through increased, tremor-related afferent input.

Second, cognitive load amplified tremor by strengthening the connectivity between the cognitive network and the cerebello-thalamo-cortical circuit. The stimulatory (i.e. exciting) nature of this effect contradicts the idea that tremor increase is the result of cognitive distraction, that is, disinhibition by cognitive control regions that in the resting state inhibit tremulous activity. Instead, the increased coupling between a cognitive and a motor network, as observed here, fits with emerging evidence that Parkinson's disease is associated with increased network-level integration in the hypodopaminergic state (Shine *et al.*, 2013, 2019), and increased between-networks connectivity as compared to healthy controls (Kim *et al.*, 2017). This may be explained by a role of dopamine in disentangling or decorrelating neighbouring circuits (Nieuwhof and Helmich, 2017), by compensatory mechanisms (Shine *et al.*, 2013), or both. Furthermore, we have previously shown that increased overlap between cognitive and motor networks at the level of the striatum was associated with impaired dual tasking (Nieuwhof *et al.*, 2017). Interestingly, it was recently shown that (in addition to dopamine depletion) increased levels of noradrenaline also support a pro-integration state of cerebral networks (Shine, 2019). Taken together, these findings suggest that tremor amplification during cognitive load may be explained by entangled cognitive and motor networks, which may be stimulated by concomitant noradrenaline release.

Translational implications

Our findings demonstrate that tremor severity is critically dependent on cognitive load, but the implications of these findings go well beyond tremor. Specifically, behavioural studies have shown that many other motor symptoms in Parkinson's disease worsen during stress, such as bradykinesia (Blakemore *et al.*, 2018) and freezing of gait (Shine *et al.*, 2013; Nieuwhof *et al.*, 2017). Levodopa-induced dyskinesias also tend to worsen under stressful circumstances, and can be alleviated by relaxation strategies. It remains to be tested whether the impact of cognitive load and stress is similar for all motor symptoms and for the adverse effects of medication, whether similar mechanisms apply, and whether these effects can be treated.

We previously showed that tremor during cognitive load is not as sensitive to levodopa as tremor during rest (Zach *et al.*, 2017). This begs the question whether there are alternative treatment options that could target the noradrenergic influence on tremor. Previous research has shown that both pharmacological agents that inhibit the noradrenergic system (such as beta blockers) and cognitive interventions (such as relaxation-guided imagery) can reduce tremor (Marsden and Owen, 1967; Schlesinger *et al.*, 2009). Furthermore, some studies suggest that mindfulness or yoga-based interventions, which modulate activity in cognitive networks (Tang *et al.*, 2015), can also reduce motor symptoms in Parkinson's disease (Pickut *et al.*, 2015; Kwok *et al.*, 2019). In healthy subjects, mindfulness reduced physiological stress responses and altered attentional network activity during an arithmetic task similar to the one used here (Tang *et al.*, 2007). Our findings suggest that these bottom-up noradrenergic interventions and top-down cognitive interventions may successfully attenuate Parkinson's tremor by acting on the thalamus. Whether or not these mechanisms apply to the same patients in a similar manner remains unclear.

An issue that remains to be solved is whether cognitive load can, in some circumstances, also reduce tremor. For instance, in our own clinical practice, some patients mention that their tremor is reduced during a concentrated, but rewarding state (such as work that they love or playing a musical instrument); this state is also called 'flow' (Cheron, 2016). This suggests that it is not actually cognitive 'load' that is necessarily detrimental for tremor, but rather a negative valence combined with arousal (i.e. cognitive stress) (de Manzano *et al.*, 2010). An elegant theory explaining this is the 2D affective space of valence and arousal (Lang, 1995), which shows that low valence in combination with high arousal leads to a stressful feeling whereas a positive valence leads to a 'flow' (in case of high levels of arousal) or relaxation (in case of low levels of arousal). Tremor increase during cognitive load may be the result of the former, whereas the latter may lead to tremor decrease. An interesting future topic would be to test how cognitive load and valence each influence tremor, and whether it is possible to teach patients to enter a state that optimally reduces their tremor.

Interpretational issues

Although we had two independent measures that have been shown to be reliable proxies of ascending arousal system activity (likely including noradrenergic afferences) (Gilzenrat *et al.*, 2010; Nassar *et al.*, 2012; Eldar *et al.*, 2013), we did not have a direct measure of activity of the noradrenergic system. Future pharmacological studies manipulating the noradrenergic system (for example via beta-blockers or atomoxetine) may confirm the role of noradrenaline on the reported effects.

Our behavioural and functional MRI results clearly indicate that patients performed the task, but it remains elusive whether this task reflects cognitive load, psychological stress, or both. However, this study was not set up to differentiate between these phenomena, and it might be hard to distinguish between both, given that they are highly dependent.

Specifically, according to the Yerkes-Dodson relationship, optimal cognitive performance is associated with intermediate levels of arousal and is worse with too little or too much arousal (Yerkes and Dodson, 1908). A similar inverted U-shaped relationship has been observed for activity of the central executive network in relation to stress (Qin *et al.*, 2009; Weerda *et al.*, 2010). Future studies may test whether stress in the absence of a cognitive task also increases tremor.

Despite previous studies, we found no tremor change-related activity in basal ganglia (Helmich *et al.*, 2011; Dirkx *et al.*, 2017). However, in those previous studies the context (resting state) was different from the current context (alternating periods of rest and cognitive load), and this may have influenced the contribution of the basal ganglia to tremor.

Conclusion

Cognitive load amplifies Parkinson's tremor by enhancing tremulous activity in the cerebello-thalamo-cortical circuit, both via bottom-up influences of the ascending arousal system onto the thalamus and by top-down influences of a largescale cognitive control network onto the cerebello-thalamo-cortical tremor circuit. These effects may be susceptible to treatment: focused anti-noradrenergic interventions and psychological interventions aimed at attenuating cognitive overload may both be effective in treating Parkinson's tremor, and perhaps also other motor symptoms with a known sensitivity to stress or cognitive load.

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Competing interests

M.D, A.v.N., H.Z. and I.T. declare no competing interest. R.H. serves on the clinical advisory board of Cadent Therapeutics, and received honoraria from AbbVie. B.B currently serves as Associate Editor for the *Journal of Parkinson's Disease*, serves on the editorial of *Practical Neurology* and *Digital Biomarkers*, has received honoraria from serving on the scientific advisory board for Abbvie, Biogen, UCB and Walk with Path, has received fees for speaking at conferences from AbbVie, Zambon, Roche, GE Healthcare and Bial, and has received research support from the Netherlands Organization for Scientific Research, the Michael J Fox Foundation, UCB, Abbvie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020, the Topsector Life Sciences and Health, and the Parkinson Vereniging.

Supplementary material

Supplementary material is available at *Brain* online.

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