RESEARCH PAPER

Multiple changes of functional connectivity between sensorimotor areas in focal hand dystonia

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2013-307127).

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Received 28 October 2013
Revised 22 January 2014
Accepted 26 February 2014
Published Online First
4 April 2014

ABSTRACT

Background Task-specific focal hand dystonia impairs the control of arm muscles during fine motor skills such as writing (writer's cramp (WC)). Functional imaging found abnormal task-related activation of sensorimotor areas in this disorder, but little is known on their functional connectivity (FC).

Methods Resting-state fMRI and regions of interest (ROI)-voxel cross-correlation analyses were used for systematically analysing the FC between multiple ROIs within the cerebello-basal ganglia-thalamocortical network in 15 patients with right-sided WC and 15 healthy volunteers.

Results Patients with WC showed a lower positive FC of several seed ROIs (left lateral premotor cortex, left thalamus, left/right pallidum) to the symptomatic left primary sensorimotor cortex compared with controls. The FC of the left primary motor cortex to prefrontal areas, pre- supplementary motor area and right somatosensory cortex was reduced and correlated with disease severity. Several cerebellar seed ROIs (right dentate nucleus, right crus I and bilateral crus II) revealed a stronger negative FC to primary and secondary sensorimotor areas.

Conclusions An increase of negative cerebello-cortical FC at rest is in line with the hypothesis of a pathogenetic role of the cerebellum in dystonia. The deficit of positive subcortico-cortical FC indicates more generalised changes within the basal ganglia-thalamocortical motor loops beyond primary sensorimotor areas in WC. As patients with WC are asymptomatic during rest, these functional network changes could reflect an underlying abnormality or compensatory neuroplastic changes of network architecture in this disorder.

INTRODUCTION

Writer's cramp (WC) is a task-specific focal hand dystonia (FHD) presenting with loss of control over arm muscles during writing (simple WC) and other fine motor skills (dystonic WC[1 2]). The pathophysiology of primary focal dystonia is still incompletely understood.[3] Task-related functional imaging has been challenging due to confounding dystonic movements during task execution. This limitation does not apply to the investigation of the resting state when patients with task-induced dystonia (including WC) are asymptomatic. Previous positron emission tomography (PET) or fMRI studies of dystonia during rest demonstrated pathological changes in the absence of overt stimuli, for example, an abnormally high glucose metabolism in the putamen, pallidum, thalamus, motor and cerebellar areas of DYT gene-mutation carriers.[4 5] In FHD, fMRI identified an elevated resting activity in the putamen and pallidum after finger tapping.[6]

During the resting state, the functional connectivity (FC) between sensorimotor areas can be assessed. For fMRI, FC is generally defined as spatiotemporal correlations of spontaneous fluctuations in blood oxygen level-dependent (BOLD) signal between remote neurophysiological events.[7] This technique was first applied by Biswal *et al*[8] for quantifying the FC between cortical motor areas. Delnooz *et al*[9] used a similar approach to investigate the intrinsic FC in the premotor-parietal circuits. They discovered a decreased FC between the left superior parietal lobe and the left precentral region in patients with right-sided WC. Applying analogue methods for EEG, Jin *et al*[10] found a reduced coupling of EEG signals recorded from the sensorimotor and premotor cortex during finger tapping suggesting a lower FC of these areas in WC. These results were in line with an independent component analysis of resting-state fMRI signals showing a disintegration of the left primary somatosensory cortex (S1) from a sensorimotor network in patients with WC.[11]

While these studies analysed the FC of (perirolandic) cortical sensorimotor areas, task-related functional imaging in focal dystonia had also identified pathological activation in regions other than these, for example, in the basal ganglia (BG) or cerebellum.[12–14] The present fMRI study in WC patients therefore systematically investigated the resting-state FC between those regions of interest (ROIs) of the cerebello-BG-thalamocortical circuits that were abnormally activated during previous imaging. Considering the results of these investigations, we hypothesised pathological changes of FC between cortical sensorimotor areas, putamen, pallidum, thalamus and cerebellum.[4–6 9–11]

METHODS

Participants

Fifteen right-handed patients (seven females, mean age±SD: 46.1±13.3 years) with right-sided WC (five had dystonic WC) and a mean disease duration of 10.7 (range 2–27) years were consecutively recruited from our movement disorder clinic. They were compared with 15 right-handed healthy control subjects (eight females, age: 46.5±12.3 years). Patients with dystonic posturing of the hand at rest were excluded. The interval between fMRI and any previous botulinum toxin treatment was ≥3 months; six patients were botulinum toxin-naive.

To cite: Dresel C, Li Y, Wilzeck V, *et al*. *J Neurol Neurosurg Psychiatry* 2014;**85**:1245–1252.

All subjects had a normal MRI brain scan, no other neurological condition and no neuroleptic medication in the past. The patients were videotaped, and the severity of dystonia was rated using the Arm Dystonia Disability Scale (ADDS) and Writer's Cramp Rating Scale (WCRS[15]). Written informed consent according to the Declaration of Helsinki was obtained from all participants. The study protocol was approved by the institutional ethics board.

Functional data

303 T2*-weighted echoplanar images (TR/TE=2200/30 ms, voxel size $3\times3\times3$ mm^3, 36 slices, FoV 216×216 mm^2, scan time 11 min) covering the whole brain were acquired during subject's rest with an eight-channel head coil on a 3T-Achieva MR scanner (Philips, Netherlands). A high-resolution T1-weighted structural image was collected using an MPRAGE sequence. Subjects were instructed to keep their eyes closed during scanning. Head motion was minimised by foam pads.

Data were preprocessed in SPM8 (http://www.fil.ion.ucl.uk/spm) based on Matlab (Mathworks, Natick, USA). After discarding the first three images to account for magnetisation–equilibrium effects, the functional data were realigned to correct for head motion, coregistered to the structural image and normalised to the MNI space using SPM8. Normalised images were smoothed with an isotropic Gaussian kernel of 8 mm FWHM.

A ROI-based analysis of resting-state FC was done in each subject using the CONN toolbox.[16] It performs a direct investigation of FC between different ROIs of the cerebello-BG-thalamocortical circuits compared with more data-driven approaches such as group-independent component analysis. The latter allows the modulation of different parameters during the analysis (eg, number of estimated independent components) and provides information on functional network composition and integrity.[7] FC itself represents a measure of connectivity between functionally related brain areas without information on the causality or direction of influence.[7 8] Positive FC (+FC) means a positive correlation of BOLD signal-time courses between two areas while negative FC (−FC) indicates anticorrelated time courses.

The CONN toolbox calculates the low-frequency temporal correlations of BOLD signal during rest between seed ROIs and all other voxels of the brain yielding ROI-specific spatial FC maps (ROI-voxel analysis). The following bilateral seed ROIs had revealed abnormal activation in previous studies (see 'Introduction') and were selected from the *AAL*-atlas of the *WFU PickAtlas-toolbox* (http://www.nitrc.org/projects/wfu_pickatlas): primary motor cortex (precentral gyrus), primary somatosensory cortex (postcentral gyrus), lateral premotor cortex (middle frontal gyrus), supplementary motor area (SMA),

Table 1 Reduced positive functional connectivity in patients with WC compared with healthy controls ($FC_{PAT}<FC_{CON}$)

Seed ROI Target regions (BA)	MNI x	 y	 Z	t value	ΔC	Cluster size (voxels)
L lateral premotor cortex (k=180)						
L postcentral gyrus (BA 3)	−18	−40	+68	5.16	−0.2392	953
L precentral gyrus (BA 4)	−34	−26	+58	4.22	−0.2293	
L occipital lobe (BA 18)	−32	−96	−10	4.45	−0.1840	249
L primary motor cortex (k=201)						
L DLPFC (BA 10/46)	−34	+44	+16	6.49	−0.2752	806
R DLPFC (BA 10/46)	+30	+42	+10	5.37	−0.1903	907
Pre-SMA (BA 6)	+10	+26	+42	5.12	−0.2254	396
R postcentral gyrus (BA 2)	+58	−30	+40	4.75	−0.2671	335
L primary sensory cortex (k=194)						
L DLPFC (BA 10/46)	−40	+48	+16	6.04	−0.2817	602
R primary sensory cortex (k=165)						
L DLPFC (BA 10/46)	−36	+48	+18	4.97	−0.3038	237
L pallidum (k=211)						
L postcentral gyrus (BA 3), L precentral gyrus (BA 4)	−44	−24	+56	5.71	−0.1709	293
R paracentral gyrus (BA 4)	+4	−38	+72	4.96	−0.1917	211
R pallidum (k=271)						
L postcentral gyrus (BA 3), L precentral gyrus (BA 4)	−32	−26	+56	4.69	−0.2059	271
L thalamus (k=266)						
L parietal op./insula (BA 13/41)	−48	−40	+18	6.01	−0.2436	419
L precentral gyrus (BA 4/6)	−54	−2	+16	5.49	−0.2446	355
R precentral gyrus (BA 4/6)	+58	+2	+12	4.54	−0.2297	277
R precentral gyrus (BA 4)	+44	−2	+52	4.39	−0.2005	274
L precentral gyrus (BA 4)	−40	−16	+54	4.20	−0.2069	266
R thalamus (k=404)						
R precentral gyrus (BA 6),	+58	+2	+12	4.57	−0.2221	404
R parietal op./insula (BA 13/22)	+50	−8	−6	4.35	−0.1786	

Peak MNI coordinates of regions with a deficient resting-state +FC to a seed ROI in patients ($p<0.05$, FWE-corrected for multiple comparisons with a cluster extent of k voxels). Note that no reduced −FC was found in patients. ΔC = absolute difference of the averaged ROI-voxel cross-correlation coefficient in a 3 mm sphere around the peak voxel between patients and controls ('−' indicates a decreased coefficient in patients).
BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; op., operculum; ROI, regions of interest; WC, writer's cramp.

anterior, middle and posterior cingulum, putamen, pallidum, thalamus, dentate nucleus and lobulus VI, crus I and crus II of the cerebellum. The complete ROIs and not subregions were used to avoid introducing an investigator-dependent bias. The CONN toolbox can handle ROIs of different sizes.[16] This accounts for the anatomical variability of individual brains and allows analysing the FC of ROIs that are defined on an anatomical basis and not necessarily on task-specific activation clusters. In addition to the entire primary motor cortex (M1-total), we defined the representation of the right hand (M1-hand) and face (M1-face) within M1 as seed ROIs to test the FC of a clinically symptomatic (M1-hand) and asymptomatic (M1-face) cortical representation (see online supplementary material).

Several confounders were regressed from the single-subject data: (i) the six realignment parameters computed during image preprocessing, (ii) the time series of the averaged CSF signal and (iii) the averaged white matter signal. This multiple regression model minimises signal fluctuations unlikely to be related to FC.[7 16]

After temporal bandpass ($0.01\,Hz<f<0.1\,Hz$) filtering, the averaged BOLD time series was extracted from each seed ROI. Positive and negative ROI-voxel correlation coefficients were obtained by calculating all possible cross-correlation coefficients between the time series of the seed and all residual voxels in the brain and converting them to Z-scores. Voxels whose cross-correlation values statistically differed from the null distribution yielded ROI-specific FC maps. The individual subject FC maps were exported to SPM8 and integrated into a random effects model for creating ROI-specific within-group and between-group FC_{group} maps and drawing population-based inferences.

As both groups showed similar group-specific FC_{group} maps for particular seed ROIs, we focused our analyses on the differences between the two groups by contrasting the ROI-specific FC maps in a second-level group analysis. If the sign of FC is *positive* (+FC), the contrast $FC_{PAT}<FC_{CON}$ means a *reduced +FC* in patients relative to controls while in case of a negative FC (−FC), the same contrast $FC_{PAT}<FC_{CON}$ indicates an *increased −FC* in patients; and vice versa for the inverse contrast ($FC_{PAT}>FC_{CON}$).

To check whether the FC in patients correlated with the severity or duration of dystonia, post hoc multiple regression models were computed for each seed ROI using ADDS, WCRS and disease duration as covariates. For example, a positive correlation between +FC and WCRS means an increase of +FC with aggravation of dystonia (WCRS: +Corr, +FC). As the ADDS decreases with increasing dystonic symptoms, a negative relationship between +FC and ADDS would also indicate an increase of +FC with aggravation of dystonia (ADDS: −Corr, +FC).

To control for multiple testing, a cluster-based *family wise error* (FWE) correction of $p<0.05$ was applied for determining within-group and between-group FC patterns for each seed ROI (tables 1 and 2). A voxel-wise threshold of $p<0.001$ uncorrected with 50 voxels extent was reported as a trend for the group comparisons and was used to check the ROI-specific individual subject FC maps. A threshold of $p<0.05$ with an SPM-adjusted cluster correction defined a significant covariance between the ROI-specific FC and the dystonia scores (table 3).

To exclude false-positive clusters and to verify that the group-wise differences of FC refer to functionally connected areas in both groups, the between-group FC maps were masked by a composite mask from both FC_{group} maps. This masking was done post hoc for confirmation of findings and did not affect the reported whole-brain statistics.

Table 2 Increased positive ($FC_{PAT}>FC_{CON}$) and increased negative ($FC_{PAT}<FC_{CON}$) functional connectivity in patients with WC compared with healthy controls

Seed ROI	MNI					
Target regions (BA)	x	y	z	t value	ΔC	Cluster size (voxels)
Increased positive FC						
L primary sensory cortex (k=228)						
R occipital cortex (BA 19)	+28	−48	+6	4.98	+0.2801	228
R precentral gyrus (BA 4)	+50	−8	+58	4.68	+0.3485	60*
L precentral gyrus (BA 4)	−64	−6	+26	4.49	+0.2813	66*
Increased negative FC						
R dentate nucleus (k=135)						
R pre-SMA (BA 32)	+4	+12	+42	4.58	−0.1444	253
R occipital cortex (BA 17)	+14	−78	+8	4.21	−0.1627	135
R cerebellar crus I (k=194)						
R postcentral gyrus (BA 2/40)	+46	−32	+48	7.15	−0.2532	400
R premotor cortex (BA 6)	+28	−10	+58	5.17	−0.2000	194
R cerebellar crus II (k=228)						
L insula (BA 13)	−32	+8	−8	5.34	−0.1553	228
L cerebellar crus II (k=184)						
R postcentral gyrus (BA 2/40)	+44	−30	+50	5.73	−0.2473	721
R occipital cortex (BA 17)	+18	−58	−12	4.70	−0.2329	359
L sensorimotor cortex (BA 4)	−34	−30	+60	4.64	−0.2313	184

Peak MNI coordinates of regions with an increased positive (correlated) or an increased negative (anticorrelated) resting-state FC to a seed ROI in patients ($p<0.05$, FWE-corrected for multiple comparisons with a cluster extent of k voxels).
ΔC = absolute difference of the averaged ROI-voxel cross-correlation coefficient in a 3 mm sphere around the peak voxel between patients and controls ('+/−' indicate an increased positive/negative coefficient in patients).
*Reduced threshold of $p<0.001$ uncorr., k=50).
BA, Brodmann area; FC, functional connectivity; suppl., supplementary; ROI, regions of interest; SMA, supplementary motor area; WC, writer's cramp.

Table 3 Correlation between the patients' functional connectivity patterns and the duration or severity of dystonia

Seed ROI / Target regions (BA)	MNI x	MNI y	MNI z	t value	Cluster size (voxels)	r
WCRS (+Corr, +FC)						
L primary motor cortex						
R insula (BA 38)	+46	+14	−14	7.59	203	0.89
R DLPFC (BA 10/46)	+32	+36	+4	4.82	156	0.72
R postcentral gyrus (BA 2)	+64	−28	+38	3.42	208	0.65
L DLPFC (BA 10/46)	−42	+34	+16	3.00	275	0.60
WCRS (+Corr, −FC)						
R cerebellar crus I						
R premotor cortex (BA 6)	+24	−10	+48	3.54	152	0.70
R premotor cortex (BA 6)	+46	−8	+44	2.72	147	0.60
R sensorimotor cortex (BA 3)	+58	−12	+26	2.51	205	0.57
L cerebellar crus II						
L sensorimotor cortex (BA 4)	−18	−22	+60	3.06	117	0.65
ADDS (−Corr, +FC)						
L primary motor cortex						
R DLPFC (BA 10/46)	+36	+40	0	4.07	174	−0.72
R postcentral gyrus (BA 2)	+62	−26	+40	3.70	165	−0.66
L DLPFC (BA 10/46)	−44	+30	+16	3.54	252	−0.69
L thalamus						
L parietal op./insula (BA 13/41)	−44	−40	+22	3.72	391	−0.65
ADDS (−Corr, −FC)						
L cerebellar crus II						
L sensorimotor cortex (BA 3)	−18	−38	+54	4.20	225	−0.76
Duration (+Corr, −FC)						
R cerebellar crus I						
R sensorimotor cortex (BA 4)	+58	−14	+28	5.09	530	0.82
R premotor cortex (BA 6)	+50	−4	+14	4.37		0.77
R premotor cortex (BA 6)	+22	−16	+52	4.01	335	0.74
L cerebellar crus II						
R sensorimotor cortex (BA 4)	+20	−32	+68	4.90	396	0.81
L sensorimotor cortex (BA 3)	−24	−36	+54	3.56	322	0.68

Peak MNI coordinates of regions with a significant correlation between WCRS, ADDS or disease duration and the ROI-specific FC in patients ($p<0.05$, SPM cluster corrected extent of 116 voxels).
ADDS, Arm Dystonia Disability Scale; BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; r, Pearson's correlation coefficient; +/−Corr, positive/negative correlation; +/−FC, positive/negative FC; ROI, regions of interest; WCRS; Writer's Cramp Rating Scale.

RESULTS

Reduced FC

When compared with controls, patients with WC showed a lower +FC of several (sub)cortical seed ROIs (left lateral premotor cortex, left thalamus, bilateral pallidum) to the left sensorimotor cortex (SMC; table 1, figure 1). The +FC of left M1-total to the pre-SMA, bilateral dorsolateral prefrontal cortex (DLPFC) and right S1 was decreased. When only the M1 representation of the right hand was considered (M1-hand), an almost identical pattern was found (see online supplementary material). The +FC of left M1-hand to the right and (as a trend) to the left pallidum was reduced. In contrast, a deficient +FC of M1-face in patients was only detected to the right and (as a trend) the left DLPFC, but not to pre-SMA, pallidum or S1 cortex. The +FC of the left and right S1 cortex to the left DLPFC was lower in patients. A deficient +FC was revealed bilaterally between the thalamus and ipsilateral S2. The coupling of the left thalamus to bilateral M1 was also reduced.

Increased FC

There was a higher +FC of left S1 to the right occipital cortex and (as a trend) to bilateral M1 in patients (table 2). We also found an enhanced −FC of cerebellar ROIs to cortical areas (figure 2). There was a stronger (inverse) coupling of the right dentate nucleus to the pre-SMA and right occipital cortex, of the right cerebellar crus I to the right SMC and lateral premotor cortex (pre-MC) and of the right cerebellar crus II to the left insula in patients. An increased −FC of the left cerebellar crus II to the bilateral SMC and right occipital cortex was also detected while no changes of +FC were revealed for the cerebellar seed ROIs. No changes of FC were generally found for the seed ROIs in the cingulum, SMA, putamen and cerebellar lobuli VI, indicating that the current data did not contain unspecific group biases that might have affected the analyses.

Correlation analyses

Table 3 presents the t-statistics and Pearson's coefficients r for the correlation between the duration or severity of dystonia and the patients' FC values. The +FC of left M1 (figure 3) to the bilateral DLPFC and right S1 cortex increased with aggravation of dystonia (WCRS: +Corr, +FC; ADDS: −Corr, +FC). Enhanced +FC was also found between left M1 and right insula (WCRS: +Corr, +FC) as well as between left thalamus and left S2/insula (ADDS: −Corr, +FC) with more severe motor impairment.

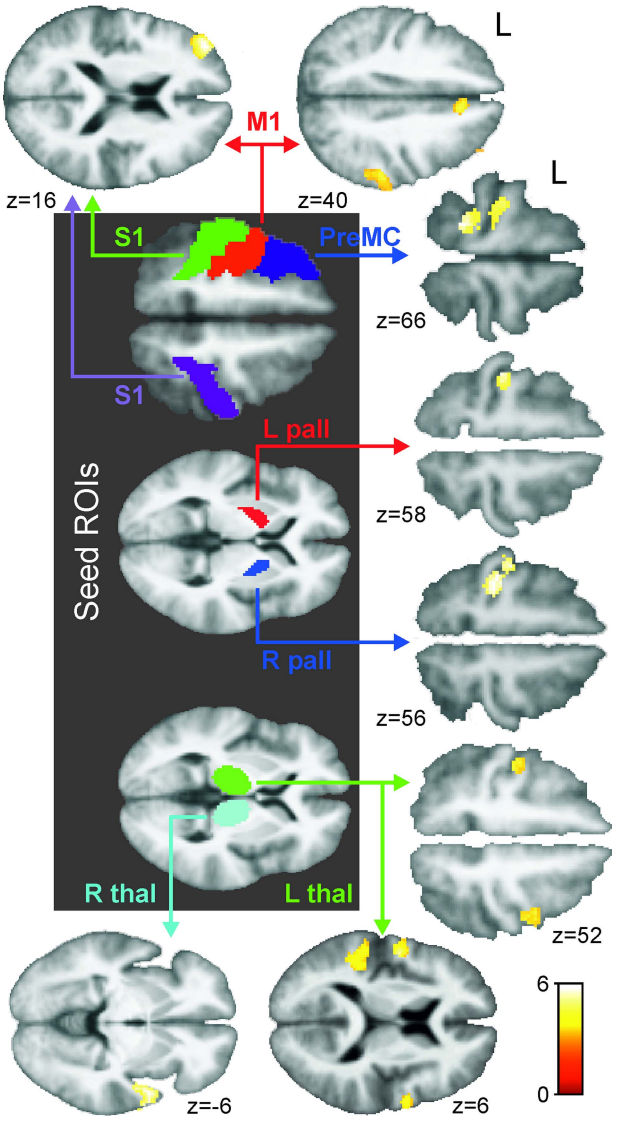

Figure 1 Reduced positive resting-state functional connectivity (FC) in patients with WC compared with healthy controls ($FC_{PAT}<FC_{CON}$): FC maps of areas (in yellow-white) with a reduced +FC to a seed regions of interest (ROI) in patients ($p<0.05$, cluster FWE-corrected), superimposed onto axial slices of the averaged structural image of all subjects (MNI z-coordinate in mm). The colour bar indicates the t values.

Regarding the cerebellar seed ROIs, the −FC of the right cerebellar crus I to the right SMC and right pre-MC showed a positive correlation with increasing severity (WCRS: +Corr, −FC) and duration (duration: +Corr, −FC) of dystonia corresponding to a decreasing magnitude of −FC. Analogue, the absolute value of −FC of the left cerebellar crus II to the left SMC decreased with greater severity (WCRS: +Corr, −FC; ADDS: −Corr, −FC) and longer duration (duration: +Corr, −FC) of disease.

DISCUSSION

This study showed that abnormal resting-state FC in WC is not limited to cortical sensorimotor areas but also involves subcortical and cerebellar regions within the cerebello-BG-thalamocortical circuits. The FC of the (clinically symptomatic) left SMC and right cerebellar hemisphere seemed to be particularly affected.

As our patients were asymptomatic at rest, the reported network changes were not confounded by dystonic activity. Earlier findings of an abnormal glucose metabolism at rest in presymptomatic DYT gene-mutation carriers suggested that a pathological resting state could represent a permissive predisposition for dystonia.[4 5] A predisposing endophenotypic trait was also discovered in the form of a maladaptive reorganisation of somatosensory representations in FHD independent from motor execution.[17 18] Along these lines, one might argue that an abnormal resting-state FC in patients with WC could similarly reflect a predisposition for developing dystonia. However, it cannot be ruled out that dystonic motor activity occurring after disease manifestation may drive secondary neuroplastic changes that could influence resting-state FC.

Several subcortical seed ROIs (left thalamus, bilateral pallidum) revealed a deficient +FC to the hand representation within the left SMC. Abnormal regional cerebral blood flow (rCBF) or activation were previously detected in these areas by task-related imaging and explained by a loss of inhibition or dedifferentiation of sensorimotor representations.[6 12–14 17–21] To date, it is unknown how these pathophysiological mechanisms relate to FC, and there is a fundamental difference between the analysis of resting-state FC and task-associated functional activation. These methods investigate different sources (spontaneous fluctuations at rest vs haemodynamic response to a task) and frequency domains (lower vs higher frequencies) of the BOLD signal.[7 8] A reduced +FC between thalamus, pallidum and left SMC reflects a deficient temporal coherence (ie, synchronisation) of their spontaneous BOLD time courses at rest while task-related imaging studies measure the task-evoked amplitude changes of rCBF or BOLD signal.

Studies of motor-evoked potentials of hand muscles in FHD patients had revealed a loss of surround inhibition.[2] Clinically, this reduces the patients' ability of suppressing activation overflow to adjacent muscles. Defective inhibition in focal dystonia was found to be generated from abnormal intracortical,[20 22] interhemispheric[23] and cerebellar mechanisms,[24 25] as well as from a putatively reduced inhibitory influence of the BG on the SMC.[21] However, it is unknown whether the spontaneous BOLD fluctuations measured in this study originate from excitatory or inhibitory neurons. Therefore, it will remain unclear how a reduced +FC between pallidum, thalamus and SMC would relate to the decreased BG-thalamocortical inhibition found electrophysiologically.

While previous studies described abnormal findings in the putamen,[4 6 13 14] the current investigation did not detect any FC changes in the putamen. A ^{11}C-raclopride PET study showed a reduced dopamine D2/D3-receptor binding during rest and a deficient endogenous dopamine release during an asymptomatic finger tapping task in the putamen of WC patients.[26] Since cortico-cortical FC seems to be modulated by dopamine as seen in Parkinson's disease, one would expect that a dysfunction of dopaminergic neurotransmission might also affect the FC of the putamen.[27] Instead, we found a deficient +FC of the bilateral pallidum to the left SMC in patients. This seems plausible as the globus pallidus is the main output station from the BG within the cerebello-BG-thalamocortical loops. An abnormal coupling of the pallidum was underlined by a post hoc analysis showing a lower +FC of the left M1-hand area to the pallidum (see online supplementary material). This is an interesting result in the context of deep brain stimulation in dystonia as the internal segment of the pallidum is the primary target of this therapy.[28]

The present finding of an impaired +FC of the left lateral pre-MC to the left SMC is congruent with the results of a

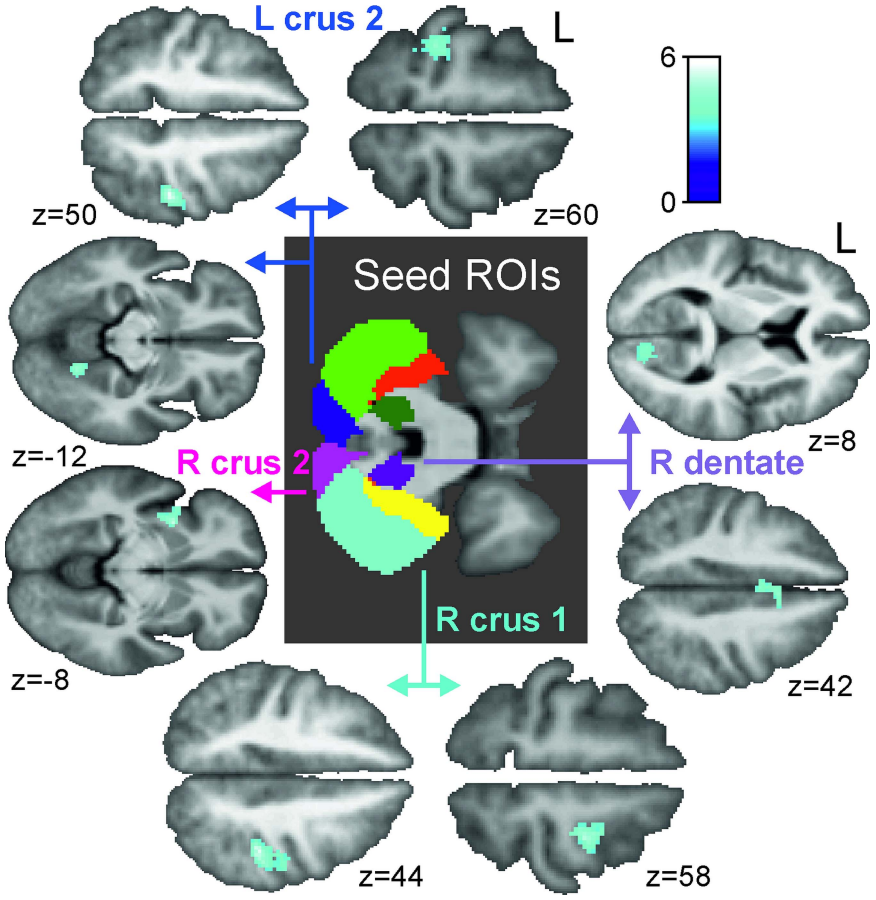

Figure 2 Increased negative resting-state functional connectivity (FC) in patients with WC compared with healthy controls ($FC_{PAT}<FC_{CON}$): FC maps of areas (in blue-white) with an increased −FC to a cerebellar seed regions of interest (ROI) in patients ($p<0.05$, cluster FWE-corrected for multiple comparisons).

recent fMRI study of premotor-parietal connectivity that detected a reduced FC between the left dorsal precentral region and the ipsilateral superior parietal cortex in right-sided WC.[9] Earlier experiments found a metabolic overactivity of the lateral pre-MC during rest,[4 5] a reduced activation during motor execution[12 13 29 30] and an increased susceptibility to repetitive TMS.[31]

In addition to previous studies, the current investigation also found a bilaterally reduced +FC between S2 and the ipsilateral thalamus in WC. When compared with the lateral pre-MC, much less is known about the role of S2 in dystonia. Task-related imaging detected an abnormal S2 activation in patients with focal dystonia.[19 32] Together with the BG and the lateral pre-MC, S2 and the thalamus participate in sensorimotor integration and motor programming. The latter has been shown to be abnormal in FHD,[33] for example, leading to an impaired force control of finger movements.[34]

Analysing the network pattern of the (at rest asymptomatic) left primary motor cortex as a seed ROI, its +FC to the pre-SMA, bilateral DLPFC and contralateral S1 cortex was impaired in WC patients. This pattern was specific for the clinically affected M1-hand representation and not found for the M1-face representation (see online supplementary material). A lower +FC between M1 and pre-SMA is in line with recent EEG findings showing a reduced β-band coupling between the sensorimotor and mesial premotor cortex during finger tapping in patients with WC.[10] The pre-SMA is engaged in the voluntary generation of self-initiated movements and was found overactive in FHD.[12] A loss of functional coupling between M1 and pre-SMA might therefore be of particular relevance for voluntary and complex motor tasks such as writing.

The DLPFC has been attributed to the acquisition of novel motor behaviour. DYT1 gene carriers had shown an insufficient activation of the DLPFC during motor sequence-learning as a correlate of disease pathology.[29] A loss of +FC between left M1 and bilateral DLPFC in WC could similarly be interpreted as an expression of disease. However, such an interpretation would not be supported by the post hoc multiple regression analysis showing a gain (instead of a pathology-related decrease) of +FC with more severe disease (table 3: WCRS: +Corr, +FC). Future studies will be necessary to clarify these issues.

The close interaction between S1 and M1 might explain why the FC of bilateral S1 to the left DLPFC is reduced, analogue to M1. Previous studies had discovered abnormal S1 responses during motor or sensory tasks in FHD.[12 19] Intermittent θ-burst stimulation over S1 reduced the pathologically increased temporal discrimination threshold for sensory stimuli in FHD patients but did not improve their writing performance.[35] In agreement to the present findings, an independent-component analysis of resting-state fMRI signals had revealed a disintegration of left S1 from a sensorimotor function network in WC.[11]

The present study found a pathologically increased −FC for some cerebellar ROIs (right dentate nucleus, right crus I, bilateral crus II) to cortical areas in patients. Negative FC means that the spontaneous fluctuations of the BOLD signal in seed (cerebellar) and target (cortical) regions were anticorrelated. Such an inverse correlation of time courses is not surprising considering the manifold excitatory and inhibitory relay stations in the connection of these areas. Although a controversy has been raised that global signal regression during fMRI data preprocessing may influence anticorrelated signal time courses leading to a false estimation of FC, the CONN toolbox does not use global

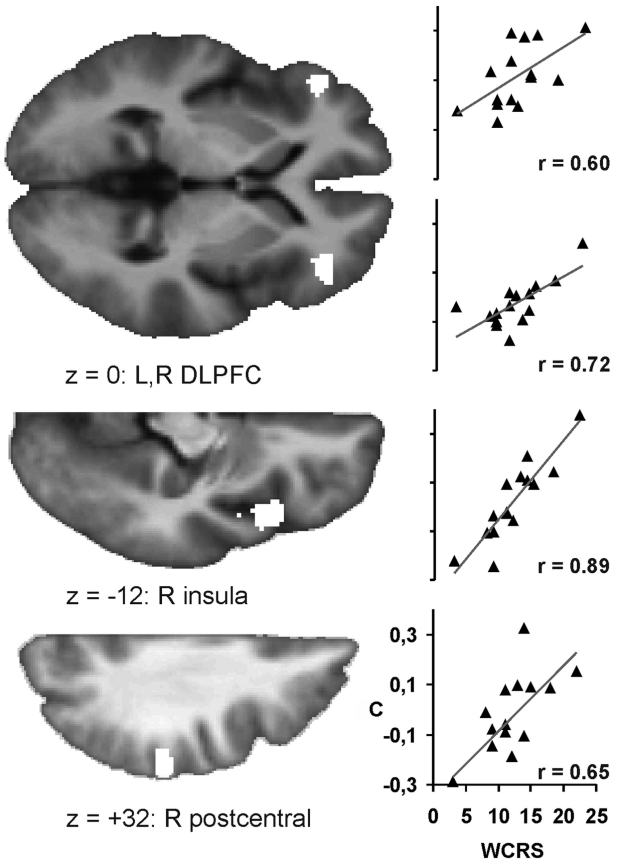

Figure 3 Correlation between the Writer's Cramp Rating Scale (WCRS) and the +FC of left M1 in patients with WC: Left column: target areas (in white) where the +FC of the left M1 cortex correlated with the severity of dystonia are superimposed onto axial slices of the averaged structural image of all subjects ($p<0.05$ with cluster-corrected extent, MNI z-coordinate in mm). Right column: regions of interest (ROI)-voxel cross-correlation coefficients (C) in a 3 mm sphere around the peak voxel of the target area indicating its functional connectivity (FC) to the seed ROI (left M1). r, Pearson's correlation coefficient of the linear fit of data.

signal regression during preprocessing and provides a correct quantification of anticorrelated FC.[16] A recent investigation confirmed that anticorrelated spontaneous fluctuations of BOLD signal indeed have a neurophysiological origin.[36]

An altered FC of cerebellar pathways is consistent with structural and functional findings from other studies in populations with different forms of dystonia. DYT gene carriers had shown a cerebellar hypermetabolism during rest[4 5] and a reduced cerebellar activation during motor execution.[29] In the same subjects, the genetic penetrance of dystonia was regulated by the degree of impairment of cerebello-thalamocortical fibre integrity.[37] Abnormal cerebello-thalamo-cortical pathways were also found in the form of a bilateral decrease of grey matter density in the cerebellum and sensorimotor cortices of FHD patients.[38] These results illustrate that the functional and structural changes of the cerebellum and its connections do not necessarily converge.

The cerebellum supports sensorimotor adaption of movements.[39] Its inhibitory influence on SMC excitability is reduced in upper limb dystonia.[24] Using different transcranial magnetic stimulation techniques, a recent study revealed that the cerebellum can influence sensorimotor plasticity in the primary motor cortex, which per se is aberrant in focal dystonia, and that this cerebellar modulation was defective in WC patients.[22 25] In contrast, the regression analyses of the current study showed that the abnormally increased −FC between cerebellar and cortical areas seems to decline with a longstanding or more severe dystonia (table 3: WCRS: +Corr, −FC; duration: +Corr, +FC). This would be a rather unexpected attribute of a pathology-related trait raising the question whether this increased cerebello-cortical −FC could result from compensatory neuroplastic changes. Such secondary neuroplastic changes might originate from dystonic motor execution and indirectly modify the resting-state functional networks.[40]

Evidence for compensatory functional changes in dystonia arises from PET studies showing increased cerebellar activation during motor sequence learning.[29 30] The decline of pathologically raised cerebello-cortical −FC with growing duration or severity of disease in our patients (table 3: WCRS: +Corr, −FC; duration: +Corr, +FC) would then be interpreted as a progressive failure of such compensatory network plasticity with increasing motor impairment. Further studies will be necessary to disentangle disease-related from compensation-induced changes of FC.

Finally, the FC of the right dentate nucleus, left cerebellar crus II and left S1 cortex to the right occipital cortex were increased. It remains speculative that a stronger coupling between sensorimotor and occipital areas could reflect an improved recruitment of visual areas since writing involves processing of visual information. Support for this interpretation comes from an fMRI study showing a stronger occipital activation as a potential compensation for a reduced tactile discrimination ability in WC patients.[14]

CONCLUSIONS

Together with the previously identified abnormalities of cortical FC,[9–11] the present findings extend the current pathophysiological concept of focal dystonia by suggesting an impaired flow of information in the form of an altered FC within the cerebello-BG-thalamocortical loops. The underlying neurophysiological origin of FC changes in WC remains to be defined. In particular, the question of how abnormal metabolism, morphometry, cortical excitability, functional activation and connectivity relate to each other could guide future studies.

Contributors Conception and design: CD and BH. Acquisition of data: CD, VW and CZ. Analysis and interpretation of data: CD, YL, FC and BH. Drafting of manuscript: CD. Revision of manuscript: all authors. Statistical analysis: CD and YL. Obtaining funding: CD and BH.

Funding This study was supported by the *Deutsche Forschungsgemeinschaft* (DFG grant number Ha 3370/3-1 to BH and CD), Bonn, Germany; and the Kommission Klinische Forschung (B10-09 to CD), Klinikum rechts der Isar, TU Muenchen, Germany.

Competing interests CD has received speaker honoraria and funding for travel from Allergan, Ipsen and Merz Pharmaceuticals. FC has received funding for travel from Allergan, Biogen Idec, Ipsen, Medtronic, Merck Serono, Merz Pharmaceuticals, Novartis and Solvay Pharmaceuticals. CZ receives research support from the DFG and the Bavarian government, AC Immune SA, Actelion Pharmaceuticals, Bayer Schering Pharma, Biogen Idec, CCBR-SYNARC, FGK Clinical Research GmbH, Genzyme Corporation, Medivation, Merck Serono, Merz Pharmaceuticals, Novartis, Quintiles and Wyeth. BH receives research support from Ipsen. He has served on a scientific advisory board for Merz Pharmaceuticals. He has received speaker honoraria from Allergan, Desitin, GlaxoSmithKline, Ipsen and Novartis and funding for travel from Biogen Idec, Ipsen, Medtronic and Merz Pharmaceuticals.

Ethics approval Ethics Committee of the Klinikum rechts der Isar, TU Muenchen.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The original functional imaging data are available at our department and can be made accessible to the editor or reviewers.

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Multiple changes of functional connectivity between sensorimotor areas in focal hand dystonia

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J Neurol Neurosurg Psychiatry 2014 85: 1245-1252 originally published online April 4, 2014
doi: 10.1136/jnnp-2013-307127