Impairment of a parieto-premotor network specialized for handwriting in writer's cramp

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ABSTRACT

Handwriting with the dominant hand is a highly skilled task singularly acquired in humans. This skill is the isolated deficit in patients with writer’s cramp (WC), a form of dystonia with maladaptive plasticity, acquired through intensive and repetitive motor practice. When a skill is highly trained, a motor program is created in the brain to execute the same movement kinematics regardless of the effector used for the task. The task- and effector-specific symptoms in WC suggest that a problem particularly occurs in the brain when the writing motor program interacts with the dominant hand. In the present MRI study involving 13 WC patients (with symptoms only affecting the right dominant hand during writing) and 15 age matched unaffected controls we showed that: (1) the writing program recruited the same network regardless of the effector used to write in both groups; (2) dominant handwriting recruited a segregated parieto-premotor network only in the control group; (3) local structural alteration of the premotor area, the motor component of this network, predicted functional connectivity deficits during dominant handwriting and symptom duration in the patient group. Dysfunctions and structural abnormalities of a segregated parieto-premotor network in WC patients suggest that network specialization in focal brain areas is crucial for well-learned motor skill.

INTRODUCTION

Writer's cramp (WC) is a form of dystonia with maladaptive plasticity, which is acquired through intensive and repetitive motor practice. Dysfunction of the basal ganglia has classically been suggested to explain dystonic symptoms; however, cortical and cerebellar deficits have now also been identified [Hallett, 2006; Quartarone and Hallett 2013]. Handwriting with the dominant hand is the essential deficit in WC patients; they can perform other motor tasks with the affected hand and can write with the non-affected hand (a different effector). The task- and effector-specific symptoms in WC suggest the occurrence of brain dysfunction only when the writing motor program is carried out by the dominant hand, thus referred to as task-specific. Note that task-specific here refers to 'writing with the dominant hand', not 'specific to writing', since writing can be performed with any limb (this usage is consistent with clinical terminology). The motor equivalence model explains that the same motor program is involved regardless of the effector used to write, all effectors having the same movement kinematics [Terzuolo and Viviani, 1979]. To explain the specificity of the symptoms in WC patients, it is critical to show that both the behavioral function and a brain network particularly involved during dominant handwriting are impaired.

Theoretical models of writing consist of two sets of processes, linguistic and motor [Roeltgen, 2003; Hillis and Caramazza, 1989; Ellis, 1982; Van Galen, 1991], each engaging different brain networks [Planton et al., 2013]. The linguistic processes are responsible for the retrieval of abstract orthographic word-forms and their storage in working memory. The motor processes are responsible for production, including letter-shape conversion, planning and ordering the sequence of letters, and the execution of specific motor programs. Given that impairments in cognitive and memory functions are absent in the phenotype of focal hand dystonia, we will focus on the motor processes that are associated with the specific deficits seen in WC patients.

Parieto-premotor cortex co-activations are observed in complex behaviors, such as speech or grasping [Fridriksson, 2010; Jeannerod et al., 1995]. When controlling for motor execution, linguistic and sensory inputs, writing specifically recruits the posterior parietal cortex, the lateral

premotor cortex and the cerebellum [Planton et al., 2013]. In healthy volunteers, parts of this network are particularly involved during dominant handwriting [Horovitz et al., 2013], suggesting these areas might support the task-specific symptoms observed in WC.

Patients with task-specific dystonia have local structural abnormalities in the lateral premotor area, the striatum and the cerebellum [Ramdhani et al., 2014; Delmaire et al., 2009]. Structural brain abnormalities in the striatum were found also in patients with cervical dystonia who do not have task-specific symptoms [Pantano et al., 2011]. Looking at structural changes alone makes it difficult to know whether they relate to primary deficits or to plastic changes following the loss of behavioural function. Multimodal imaging can contribute to show the existence of concomitant changes both in brain structure and function. Brain areas showing both specific dysfunction in dominant-handwriting and focal structural loss would likely be strong candidates to elucidate the task and *effector* specific aspect of the pathophysiology of WC.

Here, we studied the link between structural and functional changes, and how they relate to clinical signs in WC, a task-specific dystonia. Network dysfunction for task-specificity in WC patients and in unaffected healthy volunteers (HVs) in a functional magnetic resonance imaging (fMRI) study. We designed an experimental protocol [Horovitz et al., 2013] inspired by previous work [Rijntjes et al., 1999; Tertzuolo and Viviani, 1979] in which symptomatic (writing) and non symptomatic (tapping, zigzagging) tasks are executed with the symptomatic (right hand) and non-symptomatic (left hand, right foot) effectors. This complex design of nine conditions allowed isolating a task-specific network for a single task-effector combination. Here, in a new cohort of healthy subjects and a group of WC patients, we evaluated the brain activity in the areas we previously reported [Horovitz et al., 2013]. We investigated whether these areas are impaired and/or have a mis-communication during dominant handwriting in WC patients. We hypothesized that: (1) the writing program per-se is not affected in WC, but the groups differ in the RHw activation, (2) the task-specific network for dominant handwriting identified in HVs [Horovitz et al, 2013] is defective in WC; and (3) local structural integrity of the task-specific network is compromised in

WC patients.

MATERIALS AND METHODS

Subjects

Twenty-seven subjects participated in this study, including 15 healthy volunteers (HV, mean age= 54.13±10.69 years, 6 women, 9 men) and thirteen WC patients (mean age=50.5±11.3 years, 6 women, 7 men); none of the HV participated in our previous study [Horovitz et al., 2013]. All participants were right-handed as measured with the Edinburg questionnaire for handedness. Patients were diagnosed at the movement disorder clinic of the National Institute of Neurological Disorders and Stroke, had no mirror dystonia or severe dystonia at rest, and did not receive Botulinum toxin injection within 3 months before the study. The patients were carefully screened to enroll patients with homogeneous symptoms affecting only the right dominant hand. Participants had normal neurological exam (except dystonia in patients), provided informed consent according to procedures approved by the NIH Institutional Review Board and were compensated for their participation.

Experimental Conditions and Design

A digitizing tablet (fMRITouchscreen, Redwood City, CA) and a stylus were positioned at the right hand (RH) or left hand (LH) or right foot (RF; stylus fixed between the first and second toes). Subjects performed three *tasks* at a pace of one movement per second, using the stylus. They wrote (W) the sentence “THE QUICK BROWN FOX JUMPS OVER THE LAZY DOG”, tapped (T) while holding the stylus (with the whole hand or with between the first and second toes), and zigzagged (Z) back and forth movements with each of the three effectors. The tapping task was implemented as a control task to cancel out brain activation related to rhythmical movements. The

zigzagging task was an additional control to cancel out brain activation related to the spatial displacement of the effector from the left side to the right side of the tablet. These procedures allowed us to maximize the specificity of the brain network involved during writing. All participants were trained to perform all the tasks beforehand to ensure stable performance during scanning. Subjects' performances were monitored during each run through the tablet data and by visual inspection.

fMRI recordings consisted of 9 runs, one for each condition (3 tasks x 3 effectors). Each run (lasting 270 s) included 13 repetitions of the same condition for 20 s alternating with 20 s of rest. Before each run, subjects were instructed which condition to perform; the stylus was held with the corresponding effector. During the run, subjects received audio cues "start" and "relax", and had no relevant visual inputs. Head motions were monitored during scans to avoid displacement larger than 2 mm. As the stylus and tablet needed to be positioned for each effector, each run included the use of one effector to avoid body motion and one task to ensure stable performance within each group. The order of runs was randomized between subjects.

Data Acquisition

Each participant's head was stabilized in the 8-channel head coil by foam pads to avoid movements. Arms were padded to provide relaxation of proximal limb muscles. Echo planar images (EPI) were recorded on a 3.0 T General Electric MRI scanner (repetition time (TR) 1.8 s, echo time (TE) 30 ms, flip angle (FA) 90º, matrix 64 x 64 mm^2, voxel size 3.5 x 3.5 mm^2, 32 slices 4.0 mm thick, 0.5-mm gap, field-of-view (FOV) 220). A T1-weighted sequence (TR 6.836 s, TE 2.976 s, FOV 240, matrix 256 x 256, voxel size 1 x 1 mm^2, slice thickness 1.3 mm) was acquired for co-registration of EPI volumes and for the voxel-based morphometry analysis (VBM).

Data Analysis

Imaging data were pre-processed and analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm). The data were realigned to the first image of the first run, normalized to the Montreal Neurological Institute (MNI) template, and smoothed using an 8-mm Gaussian kernel. At the individual level, we estimated the amplitude of the blood oxygen level dependent (BOLD) signal comparing condition-related activity with rest (t-test) using a general linear model (GLM), thus creating nine within-subject contrasts. At the group level, these contrasts were entered in a full factorial ANOVA design with 3 factors: group (WC, HV), task (W, Z, T), effector (RH, RF, LH). The ANOVA design was used to study the simple effects of the writing program, right handwriting, and group by task by effector interaction. Significance was set at $p<0.05$, FWE corrected

Hypothesis 1: *the writing program per-se affected is not affected in WC but the groups differ in the RHw activation.*

Writing program activation: First, we computed the differences (t-test) between the levels of the factor task (W versus Z), averaging over the levels of the factors group and effector to isolate the brain areas that were more involved during writing regardless of the other factors ($p<0.05$ FWE corrected). Zigzagging was preferentially chosen as control over tapping since it has the same spatio-temporal displacements as writing. Second, we computed a conjunction contrast of the three writing tasks (RHw, LHw and RFw) for each group separately ($p<0.05$ FWE) to isolate the effect of the abstract representation of the writing motor program. Third, we tested the integrity of the writing program in patients by contrasting W-Z between groups.

For the patient group, we performed a supplementary conjunction including the non-symptomatic writing tasks (LHw and RFw), and, for both groups, a comparison of W-T and Z-T for completeness. These tests are reported in Supplementary Materials.

Right handwriting: we compared the whole brain activation and connectivity in the RHw condition between groups. The mean corrected and high-pass-filtered time series were individually extracted from the regions significantly different between groups (t-test, $p< 0.05$ FWE corrected),

and used in a functional connectivity analysis (PPI, psychophysiological interaction [Cisler et al., 2014; Friston et al., 1997]) to calculate their functional coupling with the whole brain. PPI regressors were the product of the deconvolved extracted time series and a vector coding for the main effect of condition. At the individual level, the PPI regressor, condition regressor, and extracted time series were entered in a first-level GLM model. At the group level, the 9 individual PPI t-contrasts were submitted for a group analysis in a full factorial design (2x3x3 ANOVA (group x task x effector)). We modeled the data in experimental effects (F tests) consisting of three main effects (group, task and effector) and four interactions (group x task, group x effector, task x effector, group x task x effector), setting the significance at $p<0.05$, FWE corrected.

Hypothesis 2: *the task-specific network for dominant handwriting identified in HVs is defective in WC*

We performed ROI analysis based on published results from our independent healthy volunteer cohort (N=13) studied with the same conditions and scanned with the same parameters [Horovitz et al., 2013]. In that work, we identified areas that were highly significant for RHw ($p<0.001$ FWE corrected) and non-significantly activated for any of the other eight conditions ($p>0.05$ FWE corrected for each condition). The resulting ROIs were clusters located in the left anterior putamen, left superior parietal cortex, left inferior parietal cortex, left ventral premotor cortex (PMv) and the right cerebellum.

Averaged time-courses were individually extracted for each condition (using marsbar SPM toolbox) from the ROIs with task-specific deficits. The area under the curve (AUC) of the 9 time-points corresponding to the active time after the increased slope of the HRF was tested using two-way ANOVA (interaction group x condition), setting significance at $p=0.01$, to correct for the five tested ROIs (Prism 6.0b, GraphPad Software, Inc.). In the post-hoc analyses, we tested within each group whether RHw time courses had the greatest activation amplitude compared to any other condition (positive difference and significant t-tests, $p<0.05$ Dunnett corrected), and we tested

whether RHw activation was significantly different between groups (t-tests, $p<0.05$ Bonferroni corrected).

The ROIs identified as having task-specific deficits in WC had to fulfill the following requirements: 1) the absence of group effect (t-test), 2) RHw activation smaller in WCs than in HVs, and 3) RHw activation not significantly larger than activation during the other tasks.

We studied the connectivity between the ROIs showing task-specific deficits in WC patients using dynamic causal modeling (DCM), an effective connectivity analysis (DCM10, in SPM8). Connectivity values were calculated from each individual DCM model using a GLM analysis [Friston et al., 2003]. This GLM analysis specific to DCM procedures consisted in a concatenation of the nine runs, including all the experimental conditions into a single-session model [Friston et al., 2003]. Time courses were extracted using the first eigenvariate from the user-specified mask of the regions of interest, adjusted for the effects of interest (F test) to remove the effect of the mean signal. We considered whether the connectivity values were significantly different from zero for each condition in each group (one sample t-test), and also different between groups (two sample t-test). We correlated the connectivity values with age for each groups.

Hypothesis 3: l*ocal structural integrity of the task-specific network is compromised in WC patients.*

We performed voxel-based morphometry (VBM) analysis to isolate local structural changes in the areas showing task-specific deficits in WC. Anatomical images were segmented into gray and white matter volumes. Spatial normalization of the segmented gray matter volumes and the smoothed scaled gray matter images were obtained with DARTEL toolbox (SPM8). A two-sample t-test was run using total intracranial volume, age and gender as covariates of non-interest using SPM8 to study possible difference in gray matter volumes in the areas of interest between HVs and patients ($p<0.05$ FWE corrected). In the patient group, correlation analyses (Pearson coefficient (r))

were performed between the gray matter volume in the RHw network and (i) the effective connectivity values during RHw; and (ii) clinical scores.

RESULTS

Behavior (Fig. 1)

We visually monitored that the participants correctly performed the tasks during scanning via the tablet's feedback. Patients were recruited with mild symptoms (3.42 ± 2.06 on the dystonia severity scale [Fahn, 1989]). One move per second was slow enough that the patients could perform the RHw condition for 20 s without stopping in the presence of mild symptoms, as we visually observed and they reported in a questionnaire completed after the scanning. Patients were not symptomatic during the performance of any of the tapping and zigzagging tasks, or during the writing task performed with the left hand or right foot.

Full ANOVA

In both groups, moving each effector engaged the contralateral primary motor cortex and ipsilateral cerebellum (main effect of effector, Fig. S1A). In both groups, the task activated bilateral secondary motor areas (SMA and dorsal premotor (PMd)) and parietal areas (main effect of task, Fig. S1B; S2). In the main effect of group, patients had decreased activation in the bilatera hippocampus, the right cerebellar vermis, and the right cerebellar lobule 6 compared to HVs (Fig. S1C); coordinates are reported in Supplementary Materials, Table S1. The most significant cluster for the 3-way interaction was in the left basal ganglia ([-22,-6,-6], p=0.015, cluster 38, uncorrected).

Hypothesis 1: *the writing program per-se affected is not affected in WC but the groups differ in the RHw activation.*

Writing motor program activation: First, *writing* induced an increase of activation in thesuperior parietal cortex [-22, -10, 60] compared to *zigzagging*, regardless of the factors *group* or

effector (Fig. S3). This contrast allowed removing the effect of the rhythmical and the spatial components of motor execution not specific to writing. Indeed, a larger network was isolated in the contrast writing versus tapping when only the rhythmical component was removed (see Table S3). Second, the conjunction of all the writing tasks showed that the writing program activated the SMA, the middle frontal gyrus (MFG) and the posterior parietal cortex in both groups (Fig. S4; see Table S4 for statistical results). The task effect was driven by the fact that, in both groups, SMA was more activated during writing than zigzagging and tapping (see Fig. S3), which is probably related to higher planning demands for writing compared to the other simpler tasks [van den Heuvel et al., 2003]. The same effect was observed for the MFG, a region referred to as the Exner area, previously identified as the writing area [Planton et al., 2013; Roux et al., 2009] (Fig. S3). In addition, the putamen was significantly activated for the conjunction of all writing conditions in HV, but not in WC (see Table S4).

Right handwriting: the sole significant difference between groups for the RHw comparison was in the left posterior putamen, this cluster was the most significant in the three-way interaction (see Fig. 2A-B, Table 1). The time series from this cluster seeded the PPI analysis. During RHw, the left basal ganglia functional connectivity with the left primary sensory cortex was decreased in patients compared to HVs (Fig. 2C-D, Table 1). This group difference was not observed for the other writing tasks or the other conditions.

Hypothesis 2: *the task-specific network for dominant handwriting identified in HVs is defective in WC*

Results for A.U.C. of ROIs are illustrated in Fig. 3 and summarized in Table 2. In the healthy volunteers, all the task-specific ROIs studied showed significantly larger activations for RHw than for any other tasks ($p<0.01$, Dunnett corrected), confirming our previous results. Task-specificity was not observed in the patients, meaning that, in patients, brain activation during RHw was equal or inferior to some of the other conditions. The PMv and IPC clusters were the only

clusters to show task-specific deficits in WC patients. The cerebellum and putamen clusters showed task-specificity for HVs but a generalized deficit for WC patients. SPL showed an increased level of activity in patients for all the writing conditions, though less for Rhw.

The connectivity analysis (DCM) was conducted from a fully connected model including the IPC and PMv areas, which showed task-specific activation during RHw in HV, and task-specific deficits in WC patients. The IPC and PMv areas have direct anatomical connections [Rizzolatti et and Luppino, 2001] and are involved in motor planning and in the execution of fine finger movements, respectively [Desmurget and Sirigu, 2009; Hoshi and Tanji, 2007]. Greater connectivity in the IPC-PMv network was observed during RHw than during other tasks in the HVs, but not for patients (Fig. 4B). Connectivity values from the left IPC to left PMv differed significantly from zero in each group for all RH and all writing conditions (one sample t-test, HV: $0.00001<p<0.02$; WC: $0.004<p<0.02$). During RHw, connectivity between IPC and PMv was higher for HVs than for patients ($t=4.49$, $p=0.02$; Fig. 4A). Other RH conditions and writing conditions did not show any group difference ($0.14<p<0.85$). There was a significant correlation between the reduced IPC-PMv connectivity during RHw and symptom duration in patients ($r=-0.52$, $p=0.049$): the longer the symptom duration, the lower the connectivity within the parieto-premotor network (Fig. 4B).

Hypothesis 3: *local structural integrity of the task-specific network is compromised in WC patients.*

Gray matter (GM) volume in the IPC was equivalent between groups (two-sample t-test, $p>0.05$ uncorrected), whereas patients had decreased GM volume in the hand area of the left precentral gyrus and left PMv (hand area: $T=4.01$, PMv: $T=3.95$, $p<0.05$ FWE-corrected; Fig. 5A). The GM loss in PMv correlated with the abnormal IPC-PMv connectivity ($R=0.69$, $p=0.04$; Fig. 5B), and with symptom duration ($R=-0.72$, $p=0.04$, Fig. 5C). Thus, local structural impairments in

PMv involved in the task-specific network were associated with functional abnormalities and clinical signs in WC patients.

DISCUSSION

Our study sheds more light on the pathophysiology of focal hand dystonia, showing for the first time task-dependent alteration within the dominant handwriting circuit. We showed that (1) the neural correlates of the writing program per-se wereas not affected in WC, but the groups differ in the RHw activation, in particular in the sensorimotor basal ganglia; (2) a task-specific network for the dominant handwriting [Horovitz et al, 2013] reproduced in the healthy volunteers group, but was deficient in the WC patients; and (3) local structural integrity of that task-specific network was compromised in WC patients, with these abnormalities correlating with the patients' disease duration. In contrast, the writing program network was similarly activated for both groups, regardless of the effector used to write. We suggest that a focal brain network crucial for the efficient performance of fine human skills is dysfunctional in WC patients.

Highly trained motor skills are specifically represented in selective parts of the IPC and the PMv. Engagement of a segregated parieto-premotor network during highly trained tasks requiring special dexterity is consistent with anatomical connections and intracortical recordings in monkeys [Jeannerod et al., 1995; Murata et al., 1997; Rizzolatti and Luppino, 2001]. Lesion studies highlight a specific role of the PMv in fine motor execution [Davare et al., 2006; Fogassi et al., 2001; Murata et al., 2015]. In contrast, lesions in the posterior parietal cortex induced alien hand movements, confirming that this structure is closer to motor intention and motor awareness in humans [Assal et al., 2007; Desmurget et al., 2009; Desmurget and Sirigu, 2009]. More specifically, lesions of the IPC can cause agraphia and motor planning deficits in ordering the sequence of letters [Planton et al., 2013; Scarone et al., 2009]. Furthermore, mirror neurons, which match a perceived intention

with an actual hand movement, are present in the IPC and PMv in both monkeys and humans [Rizzolatti and Sinigaglia, 2010]. Involvement of parietal and motor areas is modified by motor practice [Karabanov et al., 2012]. That study suggests that the modification of motor areas excitability via stimulation of the parietal cortex involves the premotor cortex, since posterior parietal areas heavily project to the premotor cortex, which in turn connects to M1 hand area [Rizzolatti et al., 1998; Rizzolatti and Luppino, 2001; Shields, 2016]. This promotes the idea that the parieto-premotor-M1 network specifically codes for well-trained and skillful tasks. Repetitive practice of a specific skill would contribute to its representation in the parieto-premotor network.

Repetitive and intensive practice of a specific skill is the common factor linked to the appearance of symptoms in WC. Transcranial magnetic stimulation studies had shown a loss of homeostatic control of sensorimotor plasticity in dystonic patients [Meunier et al., 2012; Quartarone et al., 2006]. Other studies have demonstrated that the integrity of the corticospinal tract originating from the pyramidal neurons in M1 is preserved in focal hand dystonia, and that abnormal increase of plasticity originates in cortical networks [Hubsch et al., 2013; Kojovic et al., 2013]. While motor practice-induced plasticity leads to increased GM volume in the healthy brain [Scholz et al., 2009; Zatorre et al., 2012], GM volume in PMv was reduced in patients proportionate to disease duration. These findings support the absence of modulation from PMv to the primary motor cortex in focal hand dystonia patients [Houdayer et al., 2012]. Disruption of premotor activation leads to an abnormal representation of hand actions [Desmurget and Sirigu, 2009]. Patients with ideomotor apraxia, who have a dissociation between the representation of hand action and its execution inducing problems in specific hand gestures, show abnormal activation and a loss of gray matter volume in the premotor cortex [Bohlhalter et al., 2009; Huey et al., 2009]. However, PMv was not reported as specifically activated during writing tasks [Planton et al., 2013]. In the meta-analyses performed on writing studies, PMv or inferior frontal gyrus activation is associated with language processes, being closely located to Broca's area in the inferior frontal gyrus [Planton et al., 2013; Purcell et al., 2011]. In the present study, the dominant handwriting task was compared to other

writing tasks with other limbs, cancelling out the effect of language processes. In addition, these meta-analyses focused on areas generally involved during writing tasks without looking at specific effect of the dominant hand, which could explain the difference with our findings. Finally, we also found a reduction of GM volume in M1 hand area contralateral to the symptomatic hand in WC patients, corroborating a previous report [Delmaire et al., 2007]. Altogether, we suggest that damage to the parieto-premotor network could originate in dysfunctional plasticity and in intensive recruitment of the motor system, including M1 hand area, in predisposed individuals.

Dominant handwriting is a skill honed since childhood to ensure efficient performance in daily activities. It associates manual dexterity and language, some core features of human cultural uniqueness that developed along evolution in parallel with the volume of the neocortex [Leroi-Gourhan, 1993]. A direct chimpanzee/human comparison showed that unique aspects of human neural responses to observed grasping were found in the PMv and IPC [Hecht et al., 2013]. Our data validate this by showing that segregated networks of the human neocortex contain a specific representation of highly trained motor skills. Focal impairments of the motor component of this parieto-premotor network are associated with the loss of efficient performance in dominant handwriting, and correlated with disease duration. Recent reviews underlined that focal hand dystonia is a pathology involving multiple networks [Lehéricy et al., 2013; Neychev et al., 2011]. The novel finding of this study is the specific involvement of a spatially restricted part of the IPC-PMv network during the symptomatic task. It is not surprising that specific impairment of an important function of the motor system is represented in a focal network of the neocortex, as it is also the case for language requiring cognitive representation and fine motor execution [Fridriksson, 2010]. This suggests that particular parts of the parieto-premotor network play an important role in highly trained motor skills.

The parieto-premotor network is a good candidate to support the representation of complex behaviors, including some parts of this network dedicated to motor skills. While within M1, the representation of muscles changes with motor expertise, the representation of well-trained manual

skills has to be stored in networks with sufficient integrative function. This is illustrated by findings on functional and structural changes within M1 and the parieto-premotor networks relative to different motor parameters. In professional piano players compared to novice participants, stronger activation in the hand area was observed during playing a piece of music [Lotze et al., 2003], a possible reflection of an increase in its cortical representation in this population that depends on the level of proficiency [Amunts et al., 1997; Schlaug et al., 2005]. Higher gray matter volumes were found in the parietal and premotor areas in professional golfer and keyboard players [Jäncke et al., 2009; Gaser and Schlaug, 2003], probably more related to action representation and visuo-spatial integration [Milton et al., 2007]. In professional ballet dancers, an effect of motor expertise was shown in ventral premotor and inferior parietal areas during action observation [Calvo-Merino et al., 2006]. Therefore, we propose that associative parieto-premotor networks are specialized in well-learned motor skills that are trained and performed on a daily basis. Disruption and alteration of this network explained task-specific deficits in WC, in addition to non-specific abnormalities in the cerebellum and the basal ganglia.

Both the associative basal ganglia and the cerebellum (vermis and lobule 6) showed impairments in WC patients that were not specific to dominant handwriting. Indeed, their activation was decreased in most of the tasks in WC patients. These results confirm the existence of non-specific basal ganglia and cerebellar dysfunction in focal hand dystonia [Fiorio et al., 2011; Hubsch et al., 2013; Moore et al., 2012]. Basal ganglia and the cerebellum have abnormal activation during asymptomatic tasks [Delmaire et al., 2005; Fiorio et al., 2011; Jankowski et al., 2013; Kadota et al., 2010; Moore et al., 2012; Wu et al., 2010] and at rest [Bharath et al., 2015; Delnooz et al., 2012; Dresel et al., 2014]. Anatomical and functional connectivity studies showed that the cerebellar vermis and the associative basal ganglia communicates with the secondary motor areas such as SMA [Bernard et al., 2012; Coffman et al., 2011; Lehericy et al., 2013]. In contrast, activation of the sensorimotor territory of the basal ganglia was specifically impaired during RHw in patients, but this area was not part of the network specifically involved during dominant handwriting [Horovitz

et al., 2013]. This suggests a non-specific role of the sensorimotor territory of the basal ganglia during dominant handwriting. The sensorimotor territory of the basal ganglia contains a somatotopic representation of the hand, and is involved in the long-term representation of complex finger sequences due to motor practice [Lehericy et al., 2005], which are both abnormal in focal hand dystonia [Delmaire et al., 2005; Gallea et al., 2015]. This suggests that WC patients have an abnormal long-term representation of well-learned sensorimotor skills, including dominant handwriting. Overall, basal ganglia and cerebellar dysfunctions are part of the pathophysiology of dystonia, but are not sufficient to explain task-specificity symptoms.

Non-specific impairments in both the cerebellum and the basal ganglia could be related to sensory defects in dystonia [Lehéricy et al., 2013; Peller et al., 2006; Quartarone and Hallett, 2013]. The cerebellum exerts powerful influences over the somatosensory system and receives direct somatosensory input from the spinal cord [Blakemore et al., 1999; Stoodley and Schmahmann, 2010]. Abnormal cerebellar modulation of the motor cortex plasticity induced by paired-associative transcranial magnetic stimulation involving somatosensory afferents was found in focal hand dystonia, at rest in absence of task-specific symptoms [Hubsch et al., 2013; Quartarone et al., 2009]. In parallel, basal ganglia play an important role in sensory gating [Kaji, 2001; Murase et al., 2000]. In our study, functional connectivity between the sensorimotor territory of the basal ganglia and the primary sensory cortex was especially decreased in patients during RHw, probaly related to abnormal somatosensory feedback processing during the symptomatic task. The sensorimotor territory of the basal ganglia and the cerebellum play an important role in the pathophysiology of dystonia, assisting the task-specific network during the execution of symptomatic task.

The superior parietal cortex is involved in the central processes for writing [Planton et al., 2013; Sugihara et al., 2006; Sakurai et al., 2007], which is confirmed by the increase of activation in this area for the contrast writing versus zigzagging in the HV group in our study. The superior parietal cortex shows a non-specific increase of activation in WC patients. Abnormal activation of the superior parietal cortex was also found in dystonic patients without task-specific symptoms

[Delnooz et al., 2013], as well as in task specific dystonia during non symptomatic tasks or at rest [Delnooz et al., 2012; Gallea et al., 2015; Kadota et al., 2010; Moore et al., 2012]. The superior parietal cortex is involved in the central processes for writing [Planton et al., 2013; Sugihara et al., 2006; Sakurai et al., 2007], which is confirmed by the increase of activation in this area for the contrast writing versus zigzagging. The language related processes for writing refer to stored knowledge about orthographic and phonological processes gained over repetitive encounters [Vingerhoets and Clauwaert, 2015], independently from the effector used to write. This suggests that this area plays a minor role in specific motor processes during online execution of dominant handwriting.

The absence of behavioral recordings during the study is a potential limitation. We enrolled patients with mild symptoms who were able to perform the symptomatic task during twenty seconds. Force and kinematic parameters are primarily coded in the primary motor cortex (M1) [Evarts 1968; Georgeopoulos et al., 1982]. Behavioral effect on brain activation due to different kinematics between patients and controls would show first in the activation level in the hand area of M1. Our results showed that there is no group difference of activation in the hand area of M1 in the main effect of group and for RHw (see supplementary material). Thus, a difference in behavior or kinemetics between WC patients and HV is unlikely to have influenced the group or the task results.

We conclude that IPC and PMv are the core elements of the network specialized in dominant handwriting, and that their specific impairments play an important role in the pathophysiology of task-specific dystonia. Individual susceptibilities in brain plasticity and environmental factors such as long-term practice can alter the structure and function of a specialized network. This study increases our understanding of how the structural organization and functional integration of focal brain networks support the encoding of well-learned motor skill. Further studies might explore whether neuromodulation therapy applied to a specialized network could improve rehabilitation of patients with task-specific disorders.

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FIGURE CAPTIONS

Figure 1. Example of the behavioral tasks performed by a patient of the WC group. RH = right hand; LH = left hand; RF = right foot.

Figure 2. Group results for RHw activation and PPI analysis. **A.** WC patients show decreased activation in the left sensorimotor (SM) putamen. **B.** Contrast estimates for the activation in all writing conditions. This cluster (1) does not show specific involvement during RHw in HV; (2) shows a significant decrease of activation during RHw in patients but not during other writing tasks. **C.** WC patients show decreased functional connectivity between the left SM putamen and the left primary somatosensory cortex (S1). **D.** Contrast estimates for the PPI analysis between the left SM putamen and the S1 in all writing conditions. This cluster shows a significant decrease of connectivity during RHw in patients but not during other writing tasks. HV: black; WC: grey.

Figure 3. Abnormal involvement of ROIs with task-specificity properties in WC patients. **A.** ROIs time courses in a total of 22 time points averaged for all subjects included in each group (n=15 for HV; n=12 for WC). **B.** AUC values together with the corresponding error-bars (SD) for all the ROIs **C.** Anatomical localization of ROIs with task specificity (see Horovitz et al., 2013 superimposed on anatomical T1 template image. PMv = ventral premotor cortex; IPC = inferior parietal cortex; Cb =cerebellar lobule 6 and 8; Putamen = anterior putamen (associative territory); SPC = superior

parietal cortex. Black: HV RHw; Grey: other eight conditions (RHt, RHz, RFt, RFw, RFz, LHt, LHw and LHz). Dark green: WC RHw; light green: WC other eight conditions.

Figure 4. Results of the connectivity analysis task-specific RHw network. **A.** Parieto-premotor connectivity specifically higher during RHw than the other RH tasks in HV but not in WC; Writing tasks performed with other effects did not show significant group difference. **B.** Parieto-premotor connectivity during RHw correlated with disease duration in WC patients. Error bars represent the standard error (SEM).

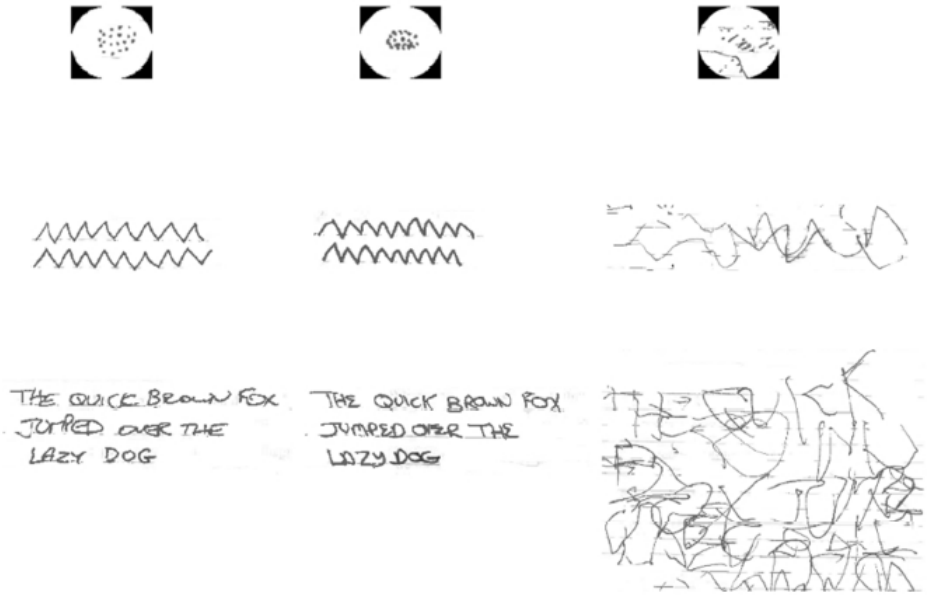
Figure 5. Local structural deficits correlate with functional connectivity impairments and symptom duration in WC. **A**. Decrease of gray matter volume in WC compared to HV in the precentral gyrus, including task specific PMv ($p<0.05$ with FWE correction for multiple comparison over the total volume of the precentral gyrus); Coordinates of global maxima in MNI space [x,y,z]= -42,-4,42; Cluster volume = 25 voxels). Loss of gray matter volume in PMv correlated with abnormal effective connectivity in the task-specificity network (**B**) and symptom duration (**C**).

Table 1: Anatomical localization of clusters and statistical results of writing program activation per group (Fig. S4) and of the PPI seeding the left posterior putamen (Fig 2). Global maxima without volume (number of voxels) values are included in the cluster of the line above. R=right, L=left, B=bilateral, BA = Brodmann area. Unc: uncorrected for multiple comparisons. FWE: Family-wise corrected.

	Anatomical localization of cluster	Coordinates of global maxima [x,y,z] (MNI space)	Z score	Cluster volume
	Activation analysis: Group x Task x Effector			
L	Posterior putamen	-22, -2, -8	2.17 (p=0.015 unc)	38
	Activation analysis: RHw HV > WC			
L	Posterior putamen	-22, -6, -8	4.51 (p=0.05FWE)	5
	PPI analysis (left posterior putamen): RHw HV>WC			
L	Postcentral gyrus (somatosensory cortex, BA 1,2)	-50, -38, 62	4.07 (p=0.05FWE)	22

Table 2: ROIs area under the curve statistics. Sign indicates the direction of the difference; positive means RHw larger than all others for task specificity, and HV larger than WC for the group comparison.

ROI	Interaction (Group by condition)	Group Paired t-test	RHw Task-specificity		RHw HV-WC
			HV sign; p-value	WC sign; p-value	sign; p-value
Ant Putamen (88 mm^3)	<0.0001	0.0004	+; <0.0001	+,- ; n.s.	+ ; <0.001
SPL (478 mm^3)	<0.0001	0.0013	+ ;<0.002	+,- ;<0.001	- ; <0.001
IPC (144 mm^3)	<0.0001	0.0807	+ ;<0.0001	+,- ; n.s.	+ ; <0.001
PMv (128 mm^3)	<0.0001	0.0953	+ ;<0.0001	+,- ;n.s.	+ ; <0.001
Cbl (2680 mm^3)	<0.0001	0.0009	+ ;<0.0001	+,- ; n.s.	+ ; <0.001



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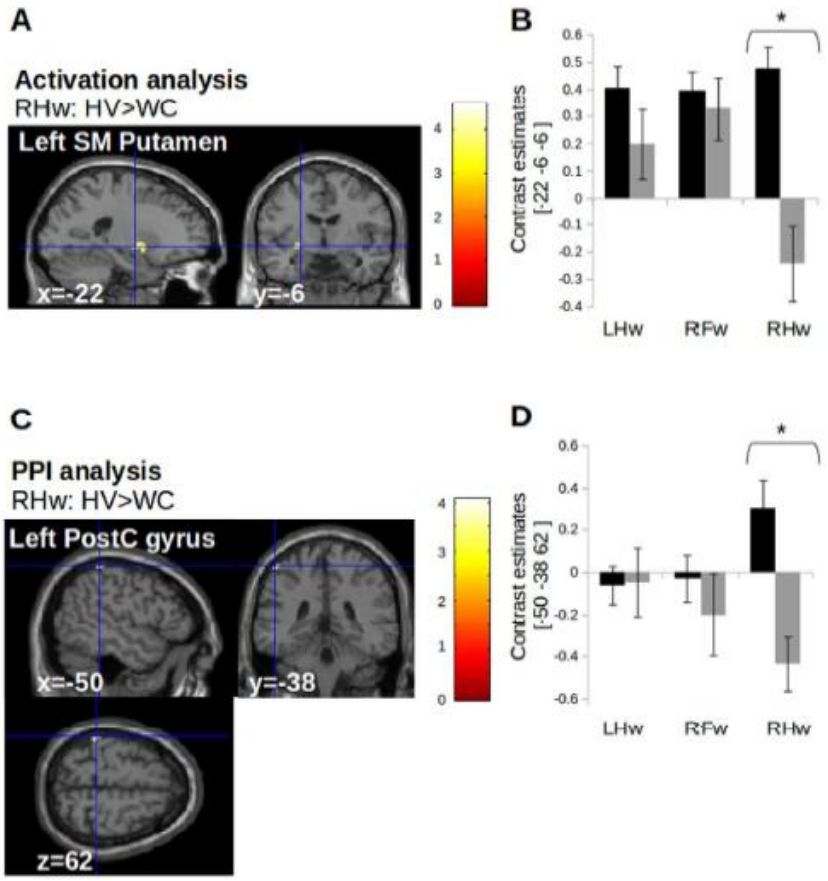

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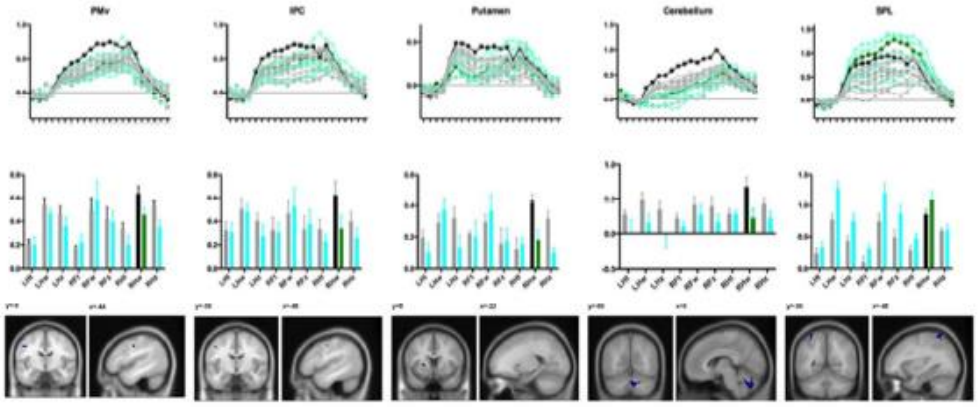

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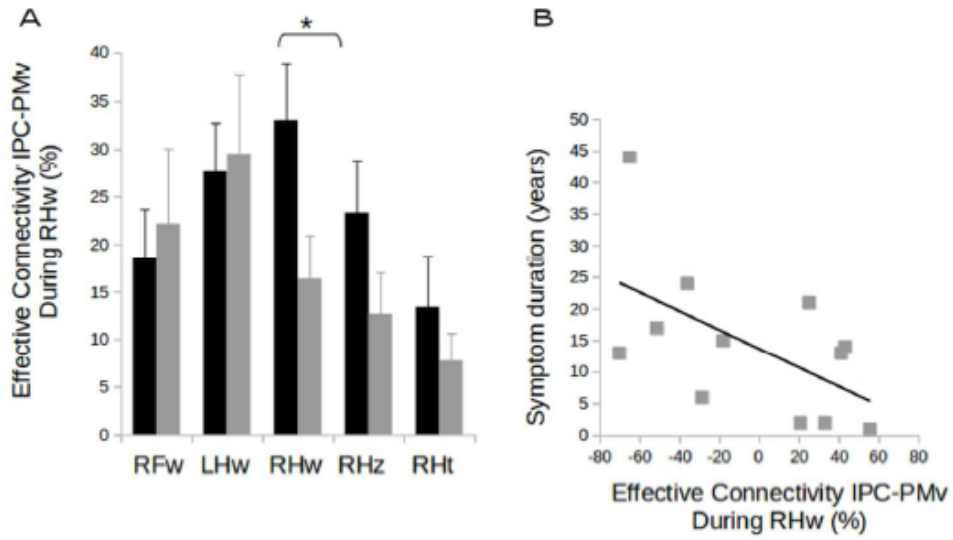

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