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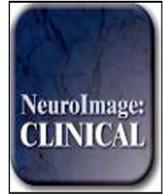
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Increased cortico-striatal connectivity during motor practice contributes to the consolidation of motor memory in writer's cramp patients



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ABSTRACT

Sensorimotor representations of movements are created in the sensorimotor network through repeated practice to support successful and effortless performance. Writer's cramp (WC) is a disorder acquired through extensive practice of finger movements, and it is likely associated with the abnormal acquisition of sensorimotor representations. We investigated (i) the activation and connectivity changes in the brain network supporting the acquisition of sensorimotor representations of finger sequences in patients with WC and (ii) the link between these changes and consolidation of motor performance 24 h after the initial practice. Twenty-two patients with WC and 22 age-matched healthy volunteers practiced a complex sequence with the right (pathological) hand during functional MRI recording. Speed and accuracy were measured immediately before and after practice (day 1) and 24 h after practice (day 2). The two groups reached equivalent motor performance on day 1 and day 2. During motor practice, patients with WC had (i) reduced hippocampal activation and hippocampal-striatal functional connectivity; and (ii) overactivation of premotor-striatal areas, whose connectivity correlated with motor performance after consolidation. These results suggest that patients with WC use alternative networks to reach equiperformance in the acquisition of new motor memories.

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1. Introduction

Writer's cramp (WC) is a task-specific form of focal hand dystonia (FHD) characterized by disruption in motor performance specifically occurring during overlearned handwriting. Retraining of sensorimotor subroutines is one of the main approaches for the rehabilitation of this

movement disorder. Therefore, understanding the mechanisms by which new motor programs are acquired and consolidated in patients with WC is crucial for improving therapeutic strategies. For now, it is not known how brain processes related to the acquisition of sensorimotor representation during motor practice are altered in patients with WC or how dysfunction in these processes would influence the consolidation of sensorimotor representation.

WC patients have impaired sensorimotor integration and maladaptive neural plasticity (Hallett, 2006; Quartarone et al., 2003; Rothwell and Huang, 2003; Tinazzi et al., 2009), which are brain processes playing a key role in the acquisition of sensorimotor representations. These deficits might be caused by structural and functional impairments of the striatum and sensorimotor cortical areas (Berardelli et al., 1998; Blood et al., 2004; Delmaire et al., 2005; Hallett, 2006; Mink, 1996; Peller et al., 2006; Vitek et al., 1999; Wu et al., 2010). However, to our knowledge, how the striatal network is involved in the acquisition of sensorimotor representations during motor practice has never been

Abbreviations: WC, writer's cramp; FHD, focal hand dystonia; HV, healthy volunteers; DT1, dual task 1; DT2, dual task 2; PD, practice dependent; CD, consolidation dependent; CV-RT, coefficient of variation for reaction time; PPI, psychophysiological interaction; FA, fractional anisotropy; RD, radial diffusivity; LD, longitudinal diffusivity; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; BA, Brodmann area.

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studied in patients with WC. Motor learning has been studied in genetic forms of dystonia, which revealed abnormal activation and structural changes in the frontal and cerebellar areas (Argyelan et al., 2009; Carbon et al., 2008). In contrast to WC, genetic dystonia develops at early age independently from intensive motor practice. In FHD patients, previous studies have reported abnormal brain activation and functional connectivity during the execution of complex finger sequences and complex finger coordination (Moore et al., 2012; Wu et al., 2010), without looking at time-dependent changes during motor practice. Time-dependent changes in brain connectivity were found during simple finger sequences with EEG, but the spatial resolution did not allow the investigation of the striatal impairments precisely (Jin et al., 2011a, 2011b). The present study aimed to investigate (i) the activation and connectivity changes in striatal and sensorimotor networks associated with the acquisition of sequential finger movements by the affected hand in patients with WC; and (ii) how these changes influence the performance of sequential finger movements after consolidation 24 h after the initial practice.

Representations of finger sequences are stored in the brain and subsequently used for successful performance (Doyon et al., 2009; Wolpert et al., 2011). Brain regions that are involved include the sensorimotor system, specifically the striatum (Doyon et al., 2009; Lehéricy et al., 2005; Ungerleider et al., 2002). In the early phase of motor practice, during which sensorimotor representations are built within a single practice session, activation decreases in the associative striatal territory (Floyer-Lea and Matthews, 2004; Jueptner et al., 1997; Laforce and Doyon, 2002; Lehéricy et al., 2005; Toni et al., 1998) and increases in the sensorimotor striatal territory (Doyon et al., 2009; Floyer-Lea and Matthews, 2004; Lehéricy et al., 2005). This functional remapping is associated with the reorganization of functional interactions in the striato-cortical networks (Coynel et al., 2010). After sleep or the simple passage of time, a consolidation phase occurs, during which sensorimotor representations are maintained or strengthened (Albouy et al., 2013a, 2013b; Dayan and Cohen, 2011; Doyon et al., 2009; Ungerleider et al., 2002). The striatum and the hippocampus are involved during the early phase of learning (Dickerson et al., 2011; Mattfeld and Stark, 2011; Schendan et al., 2003). Functional interaction between the hippocampus and the striatum during motor practice predicts the behavioral consolidation of the trained motor task performed 24 h later (Albouy et al., 2013a, 2013b, 2008). This suggests that motor skill consolidation is a continuous process relying on mechanisms that occur as early as the practice phase of motor sequence learning (Censor et al., 2014; Dayan and Cohen, 2011). Changes in striatal activation level and functional connectivity with the cortex or the hippocampus may therefore contribute to abnormal motor learning in patients with WC.

In addition to functional changes, motor practice is also associated with local structural changes of white matter fiber bundles (Dayan and Cohen, 2011; Zatorre et al., 2012). In healthy volunteers, activity in and the gray-matter volume of sensorimotor cortices predict individual learning abilities (Bueti et al., 2012). Training of patients with motor impairments induces gray matter changes within the non-affected secondary motor cortex (Burciu et al., 2013). Subcortical structural changes also affect behavioral performance in patients with hippocampal sclerosis; for instance, gray matter volume reduction in the hippocampus is correlated with decreased behavioral performance and working memory deficits (Winston et al., 2013). Altogether, functional basal ganglia impairments in patients with WC could be associated with structural changes in brain networks that usually support practice-related improvement of performance and consolidation processes.

In the present neuroimaging study, we investigated changes in the activation and functional connectivity of brain networks involved in the acquisition of sensorimotor representations of a complex finger sequence within a single practice session on day 1. We controlled for the factor of motor repetition by using a simple finger sequence. We

assessed the structural integrity of the networks involved in the practice of the finger sequences using diffusion tensor imaging and tractography. Lastly, we looked at functional and structural mechanisms that support motor performance after consolidation in patients with WC on day 2 (24 h after the initial practice). We specifically studied three main hypotheses: During motor practice, WC patients would have altered striatal activation (hypothesis 1), abnormal striatal connectivity (hypothesis 2) and an abnormal link between striatal connectivity and the consolidation of motor performance (hypothesis 3).

2. Materials and methods

2.1. Participants

Twenty-two patients with WC (mean age \pm standard deviation = 45.1 ± 15.5 years, 8 females) and 22 aged-matched healthy volunteers (HV, mean age 48.0 ± 14.9 , 8 females) participated in the study. All subjects were right-handed (i.e., had positive scores on the Edinburgh Handedness Questionnaire). The patients were recruited from the movement disorders clinic of the Fédération de Neurologie (Hôpital Pitié-Salpêtrière, Paris, France) and were diagnosed with pure WC of the right dominant hand by a neurologist (i.e., focal symptoms on fingers and/or wrist). None of the patients showed any additional neurological deficits. The duration of dystonia ranged between 3 and 34 years (mean 13.0 ± 8.9 years). The patients did not receive botulinum toxin (BTox) injections for at least 6 months preceding the study, and 2 patients were never treated with BTox. The HVs had no history of neurological or psychiatric diseases, no known learning disability, and no medical conditions that could impair fine motor performance. None of the HVs or patients was a musical instrument player or professional typist and none frequently played computer games, all conditions that do affect the level of manual dexterity. Informed consent was obtained from all participants. The experimental protocol was approved by the local Ethics Committee, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.

2.2. Behavioral tasks

Participants performed two motor tasks with their right dominant hand (which was the impaired hand for all patients): a complex motor sequence, which consisted of an 8-digit sequence (complex condition), and a simple fixed sequence (simple condition involving taping with consecutive fingers 5–4–3–2, where the index finger is “2” and the middle finger is “3”). Apart from the thumb, all fingers were equally involved in the task performance. In the complex sequence, the order of finger movements was pseudo-randomly generated using Matlab® (The Mathworks, Inc.) such that each complex sequence included two occurrences of each finger and did not include two consecutive taps with the same finger (e.g., 3–2–5–2–4–3–5–4). A given complex sequence was randomly assigned to each participant, and each participant performed the same complex sequence throughout the course of the experiment. The simple sequence was used to control for the factor of motor repetition. The simple finger sequence involved the movement of consecutive fingers, which was already represented in the brain before the beginning of motor practice, as confirmed by the lack of performance improvement in this sequence after practice (see the Results section).

2.3. Procedures (Fig. 1)

A behavioral session preceded and followed the fMRI recordings to provide a baseline before motor practice and to measure the behavioral improvement after motor practice (Fig. 1). Before scanning, subjects practiced the simple and complex conditions without metronome pacing. This familiarization phase ended when participants could perform

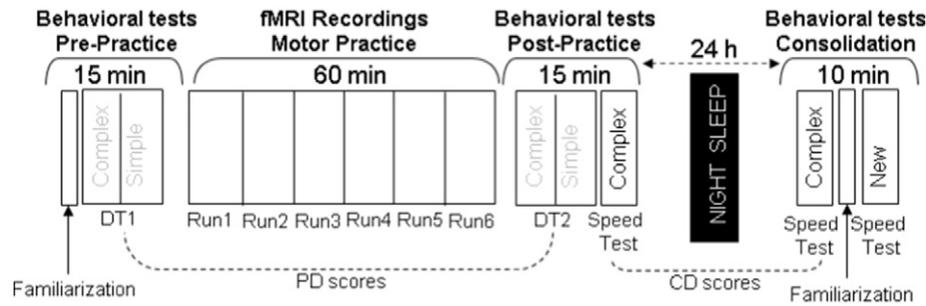


Fig. 1. Experimental design. Behavioral tests pre-practice (behavioral baseline) and behavioral tests post-practice were included to measure the practice-related improvement in behavioral performance. Motor practice occurred during fMRI recording, during which participants repetitively performed the simple and the complex sequences across 6 runs. Behavioral tests pre-practice consisted of the familiarization phase (to practice 3 sequences consecutively without a mistake) and the dual-task 1 (DT1; auditory–vocal discrimination task and sequence task) phase with the complex and simple sequences separately. The presentation of the sequence type (simple or complex) was randomized (gray police). Behavioral tests post-practice consisted of the dual-task 2 (DT2; same procedures as DT1) and speed test (to perform the complex sequence as quickly and as accurately as possible during 4 blocks of 30 s). Behavioral tests for consolidation consisted of performing a speed test for the trained complex sequence followed by the familiarization phase and a speed test for a new complex sequence.

three consecutive repetitions of the sequence without any mistake, showing that the sequence was memorized.

We assessed the acquisition of a sensorimotor representation of the complex task through motor practice by evaluating the level of automaticity of the complex sequence at the end of motor practice. Automaticity of movement is commonly investigated by studying the effects of secondary task loading on primary motor task performance (Abernethy, 1988). The conjecture is that consciously controlled movements place a substantially higher demand on working memory than automatized movements. Therefore, the execution of a secondary task is expected to interfere with performance on a consciously controlled motor task but should not – or should to a lesser extent – affect performance on an automatized task (Hazeltine et al., 2002; Kal et al., 2013). Dual-task interferences are measured through performance scores on both tasks when they are done simultaneously, with increased automatization being associated with reduced dual-task interference at the end of motor practice. Here, subjects performed a dual-task to measure baseline performance preceding motor practice (dual-task pre-practice, or DT1). Immediately after the fMRI recordings, subjects carried out a second dual-task (dual-task post-practice, or DT2) outside the scanner to quantify the practice-dependent (PD) gains in performance in the sequences, reflecting the level of task automatization (Wu and Hallett, 2008). The dual-task consisted of four 30-s blocks, each initiated by a “go” signal and terminated by a “stop” signal. During each block, participants performed the finger sequence repeatedly and continuously as quickly and as accurately as possible (primary task) while performing a verbal dissociation of auditory cues (“yes” for high tones, “no” for low tones; secondary task). The resting intervals between test blocks were constant (15 s). No feedback was provided. Behavioral measures were recorded using a 4-button response box connected to a computer for off-line analysis for the primary task and a microphone for the secondary task. Four dependent measures were calculated: (i) *motor accuracy* was the number of correct sequences out of the total number of sequences performed during the block (%); (ii) *motor speed* was evaluated using the inter-tap interval (ITI in ms); (iii) *vocal accuracy* corresponded to the number of correct answers to the tone out of the total number of stimuli (%; no answer was counted as an error); and (iv) *vocal speed* was evaluated using the reaction time (RT) corresponding to the duration between the presentation of the auditory cue and the vocal response (ms). The motor speed and vocal speed scores were computed on all the sequences, including the incorrect ones. Accuracy and speed of motor and vocal responses were combined into composite scores: the PD accuracy score ($[\text{percentage of correct verbal responses} + \text{percentage of correct sequences}] / 2$) and the PD speed score ($[\text{RT of verbal responses} + \text{ITI}] / 2$). The composite score allows measuring how the two tasks interfere with each other, taking into

account that participant could focus more on one task at the expense of the other task. The data were analyzed with SPSS 16.0.

The protocol was designed to assess brain activation during the acquisition of a sensorimotor representation of a complex sequence through motor practice. To achieve this aim, the complex sequence was learned explicitly shortly before practice. During scanning, the subjects performed the complex and simple sequences using the 4-button response box with metronome pacing at a fixed frequency of 1.5 Hz delivered through headphones (one finger tap with each auditory signal). The coefficient of variation ($CV = \sigma/\mu$) of the reaction time (defined as the duration between the auditory stimulus and the key press averaged over all finger movements within a block in seconds) and motor accuracy (as defined in the dual-task) were measured. At the beginning of each condition, participants received instructions through headphones. They heard ‘simple’ for the fixed simple sequence, ‘complex’ for the complex sequence or ‘rest’ and executed the required sequence or relaxed without moving their hand during the rest periods. During each condition (including ‘rest’), auditory signals were delivered. In each motor condition, all participants completed the same number of sequences. The fMRI acquisition included six runs, with 120 repetitions of the simple sequence and 168 repetitions of the complex sequence in total. Within each run, participants performed five blocks of simple sequences, seven blocks of complex sequences, and six blocks of rest periods (each block lasted 20 s). The order of presentation of the conditions was pseudo-randomized between runs and subjects.

To test for consolidation effects, all participants had a re-test session outside of the scanner that took place 24 h after the initial practice at the same time of the day to control for circadian rhythm effects. Consolidation-dependent (CD) scores were obtained by comparing the performance of a speed test performed after the end of the scanning session (post-training speed test) and the performance of a speed test performed 24 h after practice (+24 h speed test). The speed tests consisted of four 30-s blocks, during which participants performed the complex finger sequence repeatedly and continuously as quickly and as accurately as possible with their dominant hand, similarly to during the dual-task. Participants also performed a final speed test with a new sequence that was not practiced the day before with the same hand (speed test new). The speed test new aimed to verify that the consolidation effect was only observed for the practiced sequence and was not related to habituation to the experimental device. Two dependent measures were taken into account during the speed tests: (i) *CD accuracy* was the number of correct key presses out of the total number of sequences performed during the block (%) and (ii) *CD speed* was evaluated using the inter-tap interval (ms). The inter-tap interval was computed on all the sequences, including the incorrect ones. Consolidation scores consisted of the speed test performances after consolidation (on day

2) minus the speed test performances before consolidation (performance on day 1 after practice-related improvement).

2.4. Imaging parameters

Images were acquired using a 3 T Siemens TRIO 32-channel TIM system and a 12-channel coil for signal reception while the subjects laid in a supine position in the scanner. Thirty-six oblique axial slices covering the full volume of the brain were acquired using a gradient echo T2-weighted echo planar sequence sensitive to blood oxygenation level dependent (BOLD) contrast (TR = 2100 ms, TE = 40 ms, flip angle = 90°, voxel size = $2 \times 2 \times 3 \text{ mm}^3$, interleaved, matrix size = 64×64). All the participants were instructed to keep their eyes opened to avoid falling asleep during the fMRI recordings. High-resolution T1-weighted images were acquired for anatomical localization (TR = 2300 ms, TE = 4 ms, TI = 900 ms, 144 sagittal three dimensional MP-RAGE images, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, matrix size = 256×256). Diffusion-weighted imaging data were also acquired using high angular resolution diffusion imaging with echo planar imaging (TR = 15 s, TE = 102 ms, flip angle = 90°, b-value = 1000 s/mm^2 , 50 gradient-encoding directions, 80 interleaved axial slices, voxel size = $1.7 \times 1.7 \times 2 \text{ mm}^3$, FOV = $256 \times 256 \text{ mm}^2$, matrix size = 128×128).

2.5. Statistical analysis

2.5.1. Behavioral data

For the behavioral data recorded before and after the fMRI acquisition, we isolated the effect of motor practice on the PD performance gain (PD speed and PD accuracy) for the complex and simple sequences in both groups. These measures were entered into a repeated measures ANOVA taking into account the between-subjects factor “Group” (two levels: HV, WC) and the within-subjects factor “Motor Practice” (two levels: DT1, DT2; see Fig. 1 for acronyms). The same procedure was applied for CD speed and CD accuracy to test for consolidation effects for the complex sequence.

For the behavioral data recorded during the fMRI acquisition, we used a repeated measures $2 \times 2 \times 6$ ANOVA model (between-subjects factor “Group” (HV, WC), within-subjects factors “Condition” (complex, simple) and “Motor Practice” (Run1, Run2, Run3, Run4, Run5, Run6)) to detect main and interaction effects on the variation coefficient of the reaction time (CV-RT) and motor accuracy measures.

2.5.2. Functional MRI data

Data were analyzed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>). Anatomical images were normalized to the Montreal Neurological Institute template (final voxel size of $2 \times 2 \times 2 \text{ mm}^3$). The functional images were corrected for the subjects’ motion, normalized by using the normalized anatomical image as a reference, and smoothed with an isotropic Gaussian spatial filter (full-width half-maximum = $8 \times 8 \times 8 \text{ mm}^3$). General linear models were defined individually across runs, each with one regressor per condition. The task regressors were defined as a box-car convolved with the canonical hemodynamic response function (each block with a 20 s duration) but with parametric modulation of behavioral performance (reaction time).

Three types of second-level analyses were carried out. Analysis 1 aimed to isolate the variation in BOLD signal amplitude related to the gain in motor accuracy during the complex versus the simple conditions (i.e., identifying activated regions specifically related to the acquisition of the complex sensorimotor representation while controlling for the non-specific effects of motor practice in the simple condition). Analysis 2 aimed to isolate functional connectivity changes in striatal and hippocampal circuits that were greater during the complex condition than the simple condition. Analysis 3 aimed to isolate the brain activations or connectivity levels that correlated with the improvement in behavioral performance.

2.5.2.1. Analysis 1. We defined a full-factorial analysis in a 2-way ANOVA with 2 factors: Group (WC, HV) and Motor Practice (Run1 to Run6). The individual contrast of the complex condition versus the simple condition for each run was entered into the analysis. We tested the main effect of group, the main effect of motor practice, and the interaction Group \times Motor Practice. All main effects and interactions were tested in the entire brain as well as in regions of interest of the striatum and hippocampus according to our *a priori* hypotheses. A mask of these two regions was defined using the WFU PickAtlas (<http://fmri.wfubmc.edu/software/PickAtlas>), which was applied to the contrasts of interest. In these regions for each individual, contrast values were extracted from clusters showing significant main effects using the MarsBaR toolbox for SPM (<http://marsbar.sourceforge.net>) to test for time-specific activation changes.

2.5.2.2. Analysis 2. A functional connectivity analysis using psychophysiological interaction, PPI (Friston et al., 1997), was carried out to measure the BOLD signal co-variations between time series that were greater in the complex versus in the simple condition. We identified the areas in which the degree of coupling with the seed region was modulated specifically by the complex task compared with the simple task. The time series were extracted from binary masks of the clusters in the striatum and hippocampus showing abnormal activation patterns during motor practice. The mean corrected and high-pass-filtered time series were obtained on a subject-by-subject basis by extracting the first principal component from all time series using SPM8. The PPI regressor was computed as the element-by-element product of the de-convolved extracted time series and a vector coding for the main effect of task. The PPI regressor was mean corrected to remove subject-specific effects and convolved by the canonical HRF to account for possible hemodynamic lag. For each subject, the PPI regressor, the task regressor, and the extracted time series were entered into a first-level model. At the individual level, we tested the positive effect (t-contrast) of the PPI regressor for each run. At the group level, the individual PPI t-contrasts were submitted to a group analysis in a full-factorial design (2×6 ANOVA, Group \times Motor Practice).

2.5.2.3. Analysis 3. A multiple regression analysis was performed separately in each group to test whether activation or connectivity levels in brain networks showing main effects and interaction effects in Analyses 1 and 2 were correlated with behavioral performance during motor practice. The behavioral measures included in the model were the individual motor accuracy and CV-RT in each run of the complex condition. We also tested whether connectivity levels between the striatum and the related brain networks isolated in Analysis 2 correlated with disease duration or with behavioral performance (accuracy and motor speed) 24 h after the initial practice, which included consolidation of motor performance. In this analysis, activation and functional connectivity levels were taken from the last run of motor practice, when the sensorimotor representation was acquired. This procedure was also used in other studies (Albouy et al., 2013a, 2013b, 2008).

2.5.3. Structural MRI data

Fractional anisotropy (FA), radial (RD) and longitudinal (LD) diffusivity maps as well as fiber-tracking maps were created for each subject using FSL for data preprocessing (<http://www.fmrib.ox.ac.uk/fsl/>) and MRtrix for tractography (Tournier et al., 2007). Two analyses were carried out: a voxel-based analysis and a tract-based analysis. For the voxel-based analysis, pre-processed FA, RD and LD maps of each subject (see Supplemental material) were entered into a two-sample *t*-test using SPM8 (age and gender were added as covariates of non-interest). Group difference in FA, RD and LD was tested in the regions of interest, including the bilateral precentral gyrus, the striatum (Delmaire et al., 2009, 2005), and the hippocampus. For the tract-based analysis, we used a voxel-wise model of diffusion (the Q-ball model). The maximum likelihood solution for fiber orientation within

each voxel was represented in the form of an orientation distribution function on the location of the fiber trajectory. In the native individual space, we performed a seed-to-target analysis from regions of interest (ROIs), including the left striatum, the left hippocampus and the left precentral gyrus. For the pathway connecting the hippocampus to the striatum, the hippocampus was defined as the seed, the precommissural fornix was defined as a waypoint and the ventral striatum was defined as the target. The pathways connecting the associative (antero-dorsal) and sensorimotor (postero-dorsal) striatum to the precentral cortex (Brodmann areas 4 and 6) were defined in the left hemisphere. Tracts were reconstructed from the orientation distribution function obtained for each subject in two directions between ROIs. Dependent measures included FA, RD and LD values. We calculated the mean FA, RD and LD along each of the tracts.

A correlation analysis was performed between mean FA, RD and LD along the tracts of interest and the behavioral consolidation score as well as the disease duration for the patient group (Pearson coefficient).

2.5.4. Statistical thresholds

For behavioral comparisons, differences were considered significant when they reached a statistical threshold of $p < 0.05$.

For functional imaging, the same threshold was used for all voxel-based statistical comparisons, including fMRI contrasts and multiple regressions. Clusters were considered significantly activated at $p < 0.05$, FWE-corrected for multiple comparisons inside the volume of the whole brain or the regions for the ROI analyses.

For diffusion imaging, the same threshold was used for all the group comparisons for the voxel-based analysis and for the tract-based analysis. For the voxel-based analysis, clusters were considered significantly activated at $p < 0.05$, FWE-corrected for multiple comparisons inside the volume of the whole brain or inside the volume of the striatum and hippocampus. For the tract-based analysis, group differences in mean FA, RD and LD along the tracks were considered significant at $p < 0.05$ with Bonferroni correction. The mean FA values per tract were calculated by the product of the binary mask of each tract and the FA map of each individual. Correlation analyses between mean FA values and behavioral consolidation scores or clinical scores were considered significant when they reached a statistical threshold of $p < 0.05$.

3. Results

3.1. Behavioral data (Fig. 2)

Outside the magnet (Fig. 2A–B), the comparison of the PD speed scores and PD accuracy scores before and after the fMRI session showed that the main effect of Group was not significant [speed: $F_{1,42} = 0.73$, $p = 0.39$; accuracy: $F_{1,42} = 0.25$, $p = 0.62$]. This result indicated that the WC and HV groups' performances did not differ (Fig. 1A). There was a main effect of Condition for both PD scores [speed: $F_{1,42} = 166.87$, $p < 0.001$; accuracy: $F_{1,42} = 204.13$, $p < 0.001$], thus showing better performance levels in the simple condition than the complex condition. There was a main effect of Motor Practice for both PD scores [speed: $F_{1,42} = 131.35$, $p < 0.001$; accuracy: $F_{1,42} = 13.2$, $p = 0.001$], showing that better performance levels were achieved after scanning than before scanning. The interaction Motor Practice \times Condition was significant only for the PD accuracy score [speed: $F_{1,42} = 0.16$, $p = 0.68$; accuracy: $F_{1,42} = 13.49$, $p = 0.001$], hence revealing that after motor practice, accuracy was improved in both groups in the complex condition, but not in the simple condition.

Inside the magnet, main effects of Condition ($F_{1,42} = 27.8$, $p < 0.001$) and Motor Practice ($F_{5,42} = 12.78$, $p < 0.001$) were observed on the CV-RT, but there was no significant Condition \times Motor Practice interaction ($F_{5,42} = 1.27$, $p < 0.30$). Thus, for both groups, the variability in RT decreased with motor practice similarly for the simple and the complex sequences, while the variability in RT was lower in the simple than in the complex sequence (Fig. 2C–D). For motor accuracy

(Fig. 1E–F), there were main effects of Condition ($[F_{1,42} = 42.16$, $p < 0.000]$) and Motor Practice ($F_{5,42} = 2.66$, $p < 0.04$) and a significant Condition \times Motor Practice interaction ($F_{5,42} = 37.83$, $p < 0.001$). For both motor accuracy and CV-RT, there were no significant Group \times Condition (accuracy: $p = 0.32$; CV-RT: $p = 0.28$) or Group \times Motor Practice (accuracy: $p = 0.42$; CV-RT: $p = 0.89$) interactions. Thus, for both groups, the variability in RT decreased with motor practice and was lower in the simple than in the complex sequence. In addition, both groups performed more correct sequences (i) at the end of motor practice and (ii) in the simple than in the complex sequence.

For the 24 h post-training test, both groups performed the new complex sequence less accurately ($F_{1,42} = 19.94$, $p < 0.001$) and slower ($F_{1,42} = 47.22$, $p < 0.001$) than the trained complex sequence (Fig. 2E). This shows that consolidation improved the performance of the practiced sequence. This effect was not due to habituation to the experimental device because the performance of the new motor sequence was slower and less accurate than the trained motor sequence. The two groups performed the speed tests with equal CD accuracy (main effect of group: $F_{1,42} = 0.02$, $p = 0.93$), while the CD speed tended to be slower in patients than HVs without reaching significance ($F_{1,42} = 1.98$, $p = 0.06$; Fig. 2F). Both groups performed the complex sequence 24 h after the initial practice with better motor accuracy ($F_{1,42} = 3.55$, $p = 0.04$), while the motor speed was unchanged compared with the post-practice speed test ($F_{1,42} = 0.96$, $p = 0.33$).

3.2. Functional MRI data

Only statistically significant results as defined in the *statistical threshold* section (see the Materials and methods section) are reported in this section. Main effects and interactions for Analyses 1 and 2 are displayed in Fig. 3. The anatomical localization of the significant clusters for Analyses 1, 2 and 3 for both main and interaction effects is reported in Table 1.

3.2.1.1. Analysis 1: bold signal amplitude

The whole brain analysis showed a significant main effect of Group. Patients had greater activation in the left dorsal premotor cortex (PMd), the left ventral premotor cortex (PMv) and bilateral supramarginal gyrus (BA 40) during the complex task compared with the HVs (Fig. 3A–B). There was no significant effect of Motor Practice or Group \times Motor Practice interaction at a corrected threshold over the whole brain ($p < 0.05$ FWE).

The region of interest analysis on the hippocampus showed a main effect of Group. Compared with the HVs, patients also showed a decrease in activation in the left anterior part of the hippocampus during the complex task (Fig. 3C–D). Abnormal activation of the hippocampus in patients was explained by a sustained deactivation of the hippocampus throughout motor practice of the complex task, whereas deactivation was progressively reduced in the HVs (Fig. 3D). Post-hoc analysis on contrast values extracted with MarsBaR showed a significant effect of Motor Practice ($F_{5,42} = 11.59$, $p = 0.002$) but no significant Group \times Motor Practice interaction ($F_{5,42} = 3.10$, $p = 0.08$).

The region of interest analysis on the putamen showed a significant main effect of Motor Practice. The left posterior dorsal putamen, which corresponded to the sensorimotor territory of the striatum, had an increase in activation throughout motor practice (Fig. 3E). There was no significant effect in the anterior putamen. Post-hoc analysis on contrast values extracted with MarsBaR confirmed the significant main effect of Motor Practice ($F_{5,42} = 6.69$, $p = 0.014$; increase in activation throughout motor practice) and additionally showed a significant Group \times Motor Practice interaction ($F_{5,42} = 10.11$, $p = 0.003$) (Fig. 3F). The Group \times Motor Practice interaction showed that the HVs had increased activity in the sensorimotor putamen with motor practice, while the patients had constant activation throughout motor practice in the same area (with higher activation at the beginning

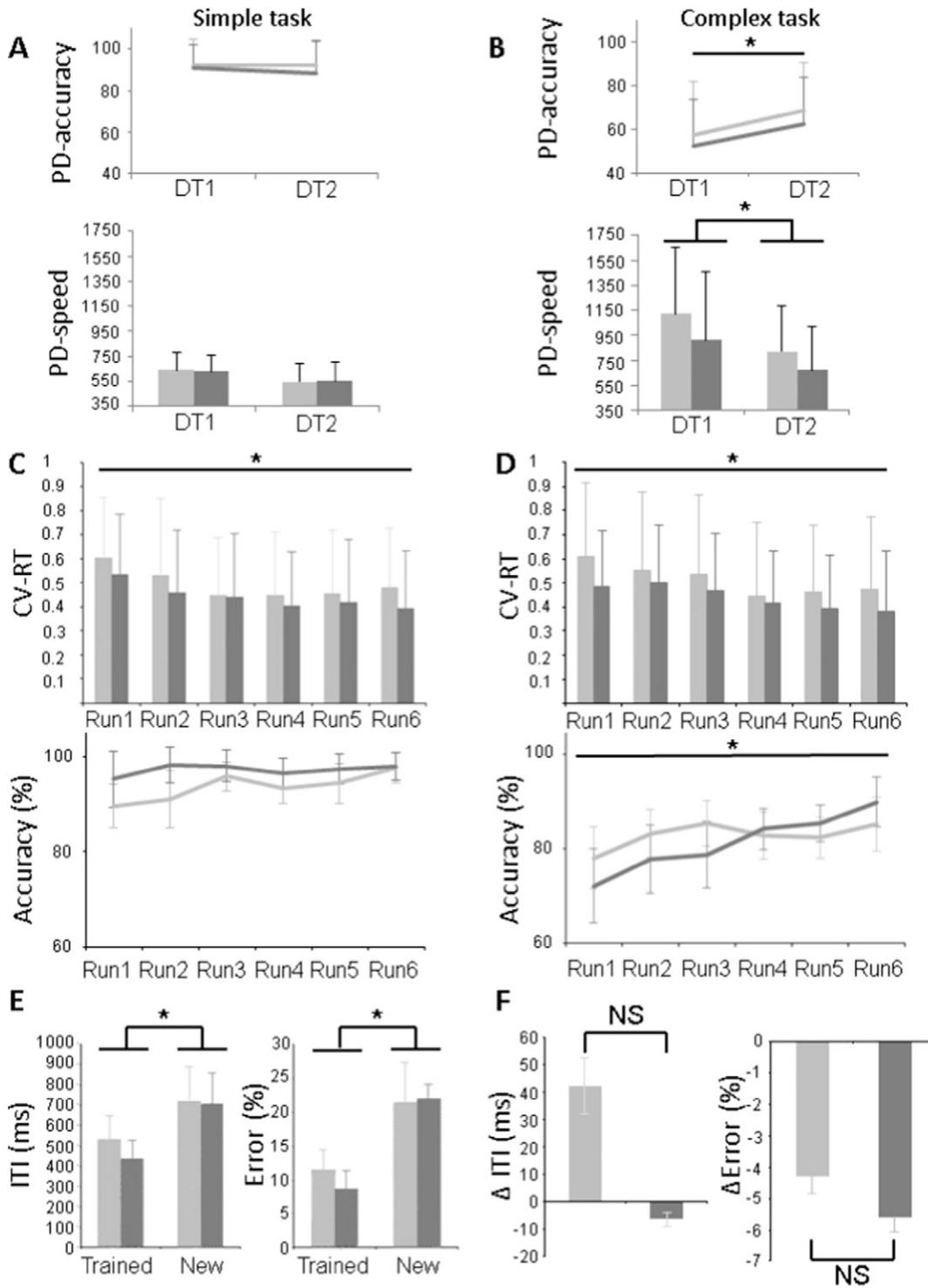


Fig. 2. Behavioral results. Significant results are indicated by asterisks ($p < 0.05$). A–B. Changes in performance between dual-task 1 preceding motor practice (DT1) and dual-task 2 following motor practice (DT2). Histograms show practice-dependent speed scores (PD-speed). Plots show accuracy scores (PD-accuracy = percentage of correct responses) for the simple (A) and the complex (B) sequences. C–D. Motor practice-related changes in reaction times (CV-RT) and accuracy scores (percentage of correct sequences) for the simple (C) and the complex (D) tasks during fMRI recording. Black asterisks represent the main effect of motor practice (from Run1 to Run6). E–F. Changes in performance 24 h after practice. E. Inter-tap interval (ITI, left) and accuracy scores (error = percentage of correct responses, right) for the complex (Trained) and the new (New) sequences on day 2. F. Consolidation-dependent accuracy and speed scores (speed test performance 24 h after the initial practice on day 2 minus speed test performance at the end of practice on day 1) for the complex task.

of motor practice in the WC patients than in the HVs; Fig. 3E). We verified that activity in the sensorimotor putamen remained constant over time in both groups during the simple task (see Supplemental material and Supplemental Fig. 1), meaning that the motor practice-related increase in activation was due to the complex task.

3.2.1.2. Analysis 2: functional connectivity (psycho-physiological interaction)

The left dorsal putamen, which showed a main effect of Motor Practice during the performance of the complex sequence, was taken as a seed for the PPI analysis. We extracted the time course from a mask

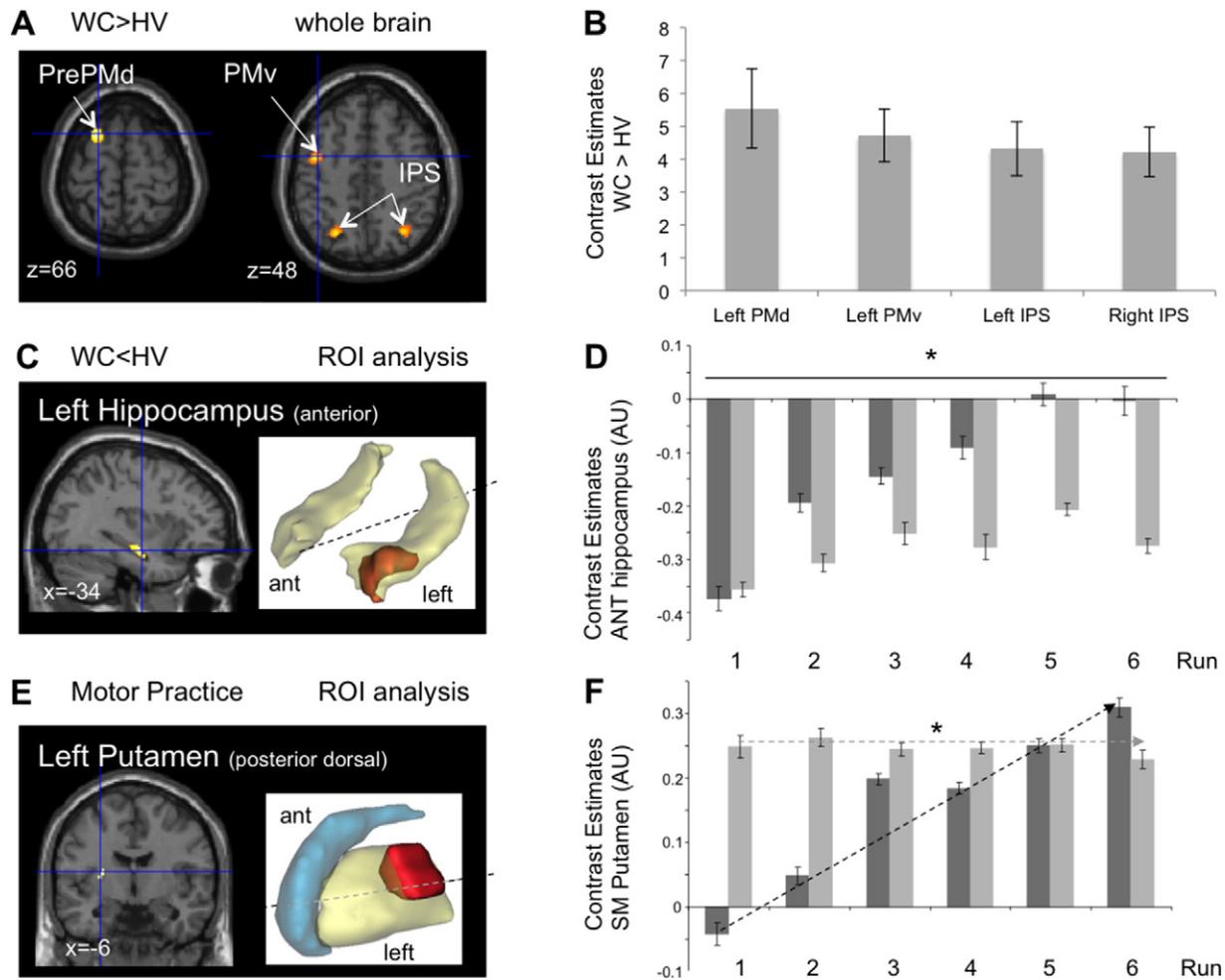


Fig. 3. Results of the 3-way ANOVA showing the main effects of Group and Motor Practice and the Group \times Motor Practice interaction detailed in Analysis 1 and Table 1. A. Activation increase in WC patients compared with HVs in the cortex (main effect of group, $p < 0.05$, FWE correction over the whole brain). B. Contrast estimates in clusters shown in A. C. Activation decrease in WC patients compared with HVs in the left anterior hippocampus (main effect of Group, $p < 0.05$, FWE correction at the ROI level). D. Contrast estimates in the left anterior hippocampus (cluster displayed in C), showing a significant effect of Motor practice (post-hoc analysis at the ROI level). E. Main effect of Motor Practice in the left posterior putamen ($p < 0.05$, FWE correction at the ROI level). F. Contrast estimates in the left posterior putamen (cluster displayed in E), showing a significant Group \times Motor Practice interaction (post-hoc analysis at the ROI level). In D and F, histograms represent the extracted values of contrast estimates (complex-simple) for the patients (light gray) and the HVs (dark gray). The black asterisk and plain bar in D indicate a significant effect of Motor Practice in the post-hoc analysis. The black asterisk and dashed bars in F indicate a significant Group \times Motor Practice interaction. Abbreviations: PMd = dorsal premotor cortex; PMv = ventral premotor cortex; IPS = intraparietal sulcus.

including all the voxels of the cluster of the putamen isolated in Analysis 1 (cluster represented in red in Fig. 3E). There was no main effect of Group, but there was a significant effect of Motor Practice in the left intraparietal sulcus (see Supplemental Fig. 2A; Table 1). There was also a significant Group \times Motor Practice interaction, i.e., functional connectivity between the left sensorimotor putamen, the left hippocampus, and the right cerebellum (lobules 4 and 5) increased with motor practice among the HVs and decreased in the patients (Fig. 4A, Table 1).

The left anterior hippocampus, which showed a main effect of Motor Practice during the performance of the complex sequence, was also taken as a seed for the PPI analysis (cluster represented in red in Fig. 3C). There was a significant main effect of Group: WC patients had a decrease in functional connectivity between the left hippocampus, the bilateral supplementary motor area and the left parietal operculum corresponding to the secondary sensory area compared with the HVs (see Fig. 4B; Table 1). There was no significant effect of Motor Practice or Group \times Motor Practice interaction.

3.2.1.3. Analysis 3: multiple regressions

There was no significant correlation between brain activation and the consolidation of behavioral performance in either of the two groups ($p > 0.05$). In the HVs, functional connectivity between the sensorimotor

putamen and the anterior hippocampus during the last run of motor practice (when a sensorimotor representation was acquired) predicted the improvement in CD accuracy score after consolidation of motor performance ($r = -0.75$, $p < 0.05$; Fig. 3D). This was not observed in the patients ($p > 0.05$; Supplemental Fig. 2B). Instead, in the WC patients, functional connectivity between the putamen and the PMd during the last run of motor practice (i.e., when a sensorimotor representation is built) predicted the CD accuracy score after consolidation of motor performance ($r = 0.70$, $p < 0.05$; Fig. 3C, plot in Fig. 3E), which was not observed in the HVs ($p > 0.05$; Supplemental Fig. 2C). Functional connectivity between the putamen and PMd during the last run of motor practice also correlated with the disease duration ($r = 0.58$, $p < 0.05$; Fig. 4F).

3.3. Diffusion MRI data

In the WC patients, a decrease in FA was observed in the left sensorimotor territory of the putamen and the left ventral premotor area compared with the HVs (ROI analysis, Supplemental Fig. 3A). Other measures did not show significant differences between groups ($p > 0.05$, uncorrected). There were no group differences in mean FA, RD or LD along the hippocampal–striatal or precentral–striatal tracts

Table 1

Anatomical localization of clusters and statistical results of the analysis of functional MRI data and the voxel-based analysis of fractional anisotropy (FA). Global maxima (coordinates in MNI space) without volume (number of voxels) values are included in the cluster of the line above. WC = writer's cramp patients; HV = healthy volunteers; BA = Brodmann area; L = left; R = right; B = bilateral.

Anatomical localization of cluster	Brodmann area	Hemisphere	Coordinates of global maxima			Z score	Cluster volume
			x	y	z		
Analysis 1							
Main effect of Group:							
WC > HV							
<i>Frontal</i>							
Superior frontal gyrus, PMd	BA6	L	−20	12	66	4.92	141
Precentral gyrus, PMv	BA6	L	−40	0	48	4.22	36
<i>Parietal</i>							
Superior parietal cortex, intraparietal sulcus	BA7	L	−24	−64	50	4.38	
Precuneus	BA7	L	−16	−70	60	5.08	106
Inferior parietal cortex, supramarginal gyrus	BA40	R	36	−34	40	4.27	30
Main effect of Group:							
WC < HV							
Anterior hippocampus		L	−34	−10	−16	3.45	143
Main effect of Motor Practice:							
Run1 < Run2 < Run3 < Run4 < Run5 < Run6							
Posterior dorsal putamen		L	−28	−6	12	4.47	40
Analysis 2							
<i>Seed = Left sensorimotor putamen</i>							
Interaction Group × Motor Practice:							
[Run1 < Run2 < Run3 < Run4 < Run5 < Run6]_{HV} > [Run1 < Run2 < Run3 < Run4 < Run5 < Run6]_{WC}							
Posterior hippocampus		L	−16	−30	−8	4.39	15
Anterior hippocampus		L	−30	−10	−8	3.90	18
Cerebellum (lobules 4 and 5)		R	28	−38	−28	4.07	34
<i>Seed = Left anterior hippocampus</i>							
Main effect of Group:							
WC < HV							
Supplementary motor area (BA6)		B	2	2	62	4.12	260
Parietal operculum (S2)		L	−52	−26	22	3.82	125
Analysis 3							
Positive correlation with CD accuracy and functional connectivity with putamen (WC)							
Precentral gyrus (M1 hand area)		L	−26	−24	54	3.22	45
Precentral gyrus (PMv)		L	−40	4	48	3.17	210
Precentral gyrus (PMd, SMA)		L	−14	−12	62	3.12	68

(Fig. 5B; $0.02 < T < 0.35$, $0.54 < p < 0.91$). The mean FA along the hippocampal–striatal tract correlated with the CD accuracy score in the HVs ($r = 0.55$, $p = 0.03$; Fig. 5C) but not in the patients (Supplemental Fig. 3B), i.e., higher mean FA values correlated with a higher number of correct sequences during the 24 h post-training test compared with the immediate post-training speed test. In the patients but not in the HVs, the mean FA along the tract connecting the left precentral gyrus and the putamen (associative territory) correlated with the CD speed after consolidation of motor performance ($r = -0.69$, $p < 0.05$; Fig. 5D, Supplemental Fig. 3C), i.e., higher mean FA values correlated with a reduced inter-tap interval. The mean FA along the tract between the precentral gyrus and the associative putamen also correlated with the disease duration ($r = 0.55$, $p < 0.02$; Fig. 5E).

4. Discussion

During the acquisition of sensorimotor representations through motor practice, patients with WC had (i) abnormal activation of the sensorimotor putamen; (ii) reduced hippocampal activation and hippocampal–striatal functional connectivity; and (iii) overactivation of premotor–striatal areas, whose connectivity correlated with consolidated motor performance 24 h after the initial practice. These results suggest that in WC patients, an alternative associative cortico-striatal circuit supported the acquisition and consolidation of new motor memories to compensate for altered sensorimotor striatum and hippocampus circuits.

We found an abnormal involvement of the sensorimotor putamen during the acquisition of a sensorimotor representation in WC patients characterized by over-recruitment at the beginning of motor practice and absence of practice-related dynamic changes in activation. In HVs, motor practice was associated with the expected increase in activation in the sensorimotor territory of the putamen (Fig. 3E), as shown in previous studies confirming striatal involvement in the long-term retention of well-learned sequences of movements (Doyon et al., 2009; Floyer-Lea and Matthews, 2004; Jueptner et al., 1997; Lehericy et al., 2005). In contrast, WC patients did not present the expected increase in activation in the left sensorimotor putamen (contralateral to the affected hand) associated with motor practice. It has to be noted that these results were independent of the factor of motor repetition, since they were obtained from the contrast of the complex versus the simple sequence. Indeed, there were no changes in performances in the simple sequence, as shown by the absence of difference between the dual-test 1 (DT1) preceding motor practice and the dual-test 2 (DT2) following motor practice. Thus, the improvement of reaction times of the simple sequence during motor practice accounted for the effect of motor repetition during the fMRI recording, and not to the acquisition of a new sensorimotor representation. In contrast, performances improved in the complex sequence at the end of motor practice, as shown by the difference between the dual-test 1 (DT1) preceding motor practice and the dual-test 2 (DT2) following motor practice. This suggested that a new sensorimotor representation was created in the brain at the end of practice. This means that the contrast of the complex versus the simple sequence allowed us to isolate brain networks involved in the newly

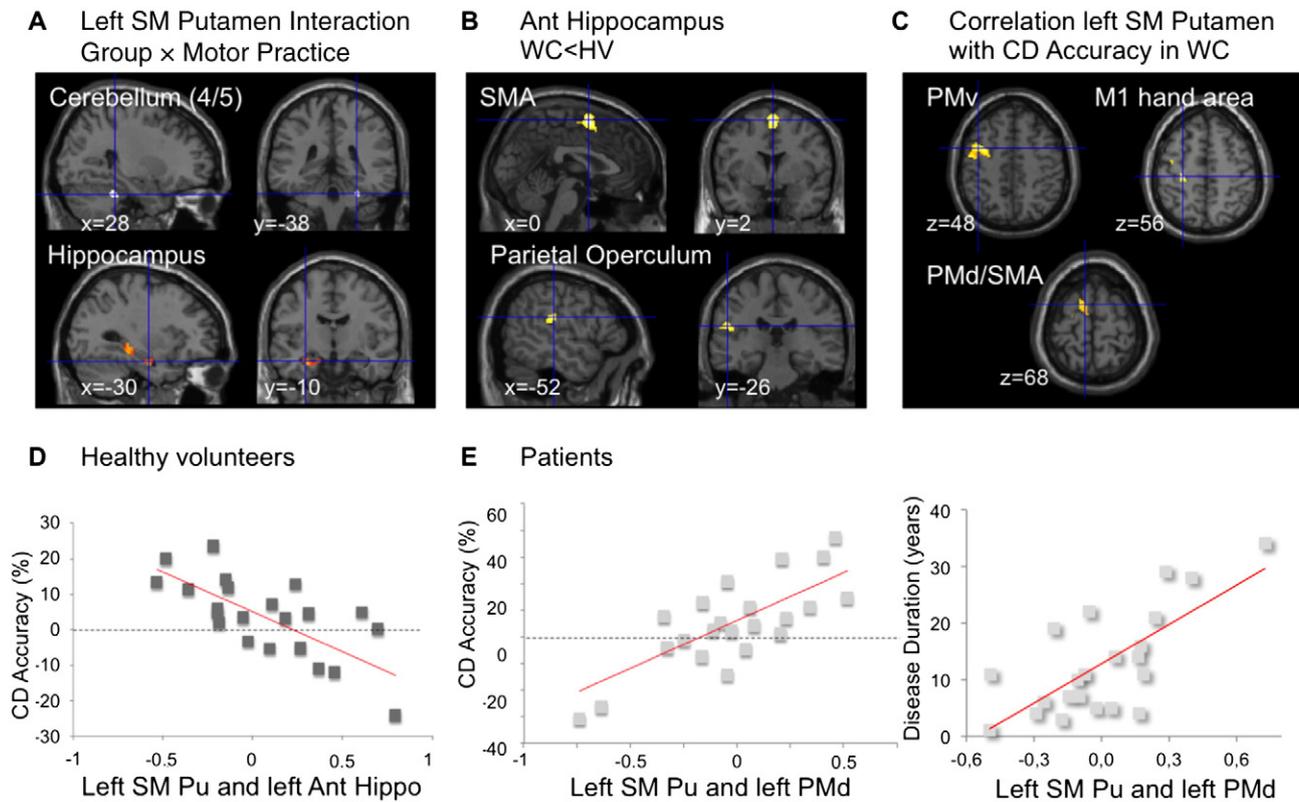


Fig. 4. Functional connectivity of striatal circuits involved in the acquisition of a sensorimotor representation. A. Results of the psychophysiological interaction (PPI) analysis, with the left posterior dorsal putamen as the seed (Analysis 2, Table 1) showing a significant interaction effect. In HVs, the left posterior dorsal putamen had a practice-related increase in connectivity with the left hippocampus and the right cerebellum; in contrast, this network had a practice-related decrease in functional connectivity in WC patients. B. Results of the PPI analysis, with the left anterior hippocampus as the seed (Analysis 2, Table 1) showing a significant main effect of group. The left anterior hippocampus had a decrease of functional connectivity with the SMA and parietal operculum in WC patients compared with HVs. C. Results of the multiple regression analysis on the PPI individual contrasts, with the posterior dorsal putamen as the seed (Analysis 3, Table 1). The ventral premotor cortex (PMv), dorsal premotor cortex (PMd) and M1 hand area showed an increase in functional connectivity that correlated with the improvement of PD accuracy in WC patients. D. Plot of the correlation in HVs between individual values of consolidation-dependent accuracy score (CD accuracy) and individual values of functional connectivity between the sensorimotor (SM) putamen (Pu) and the left anterior hippocampus (Left Ant Hippo) extracted from the cluster shown in A (Analysis 3, Table 1). E. Plots of correlations in WC patients between individual values of functional connectivity between the SM Pu and PMd extracted from the cluster shown in C (Analysis 3, Table 1) and individual values of CD accuracy (left) and disease duration (right).

acquired sensorimotor representation and not simply related to motor repetition. In addition to functional abnormalities, we also showed a decrease in FA in the putamen, which is in line with previous studies reporting structural changes in the basal ganglia in FHD (Delmaire et al., 2009, 2005). The link between diffusion and cellular changes is far from understood. Several studies have shown that fibers present in a specific orientation in gray matter and that diffusion MRI is able to detect layer-specific intracortical connectivity (Kershaw et al., 2013) and intra-basal ganglia fiber orientation (Douaud et al., 2009). FA reductions in the gray matter of the sensorimotor putamen may thus indicate changes in overall fiber orientation or a decrease in intra-basal connectivity. The populations of striatal neurons in the sensorimotor territory with preserved intra-basal connectivity may be over-recruited during the acquisition of sensorimotor representations.

WC patients showed a lack of dynamic practice-related changes in hippocampal activation, characterized by a sustained de-activation at the end of motor practice. Dynamic practice-related changes in activation in the left anterior hippocampus were observed in HVs, reproducing the results of other studies (Albouy et al., 2013a, 2013b, 2008; Gheysen et al., 2010). The hippocampus plays a role in the association of temporally non-contiguous information during motor sequence learning (Schendan et al., 2003), as individual key presses are progressively assembled into a sequence (Dayan and Cohen, 2011; Doyon et al., 2009; Gheysen et al., 2010). This suggests that patients have abnormal sequence assemblage in the hippocampus and that the sensorimotor representation is differently built up compared with HVs. To our

knowledge, hippocampal dysfunction has not been reported in dystonia either in humans or in animal models (Regensburger et al., 2009; Yokoi et al., 2009). Abnormal hippocampal functioning may be secondary to basal ganglia dysfunction or abnormal sensory processing in WC patients. In control subjects during motor practice, sensory inputs processed in the parietal cortex are transmitted to the hippocampal system, which compares current sensory inputs to previous ones that are stored in memory (Chen et al., 2011; Grecucci et al., 2010). As FHD patients have abnormal processing of sensory inputs (Dolberg et al., 2011; Fiorio et al., 2011, 2003; Hallett, 2006; Molloy et al., 2003; Sanger et al., 2001) and bilateral deficits of somatosensory representation in the parietal cortex (Meunier et al., 2001; Nelson et al., 2009), parietal inputs to the hippocampus may be abnormal. In support of this hypothesis, WC patients over-activated the parietal cortex and had reduced functional connectivity between the hippocampus and the parietal operculum.

There is increased evidence for a role of the cerebellum in the pathophysiology of FHD (Lehéricy et al., 2013; Neychev et al., 2011; Quartarone and Hallett, 2013). We did not find abnormal cerebellar activation during motor practice in WC patients. The lack of activation changes in the cerebellum may be explained by the fact that in current models of learning, the cerebellum may contribute to motor adaptation rather than to motor sequence learning (Debas et al., 2014, 2010; Doyon et al., 2009). Abnormal cerebellar activation and connections were observed in genetic DYT1 dystonia (Carbon et al., 2011, 2008). The authors suggest that patients with genetic dystonia might use increased

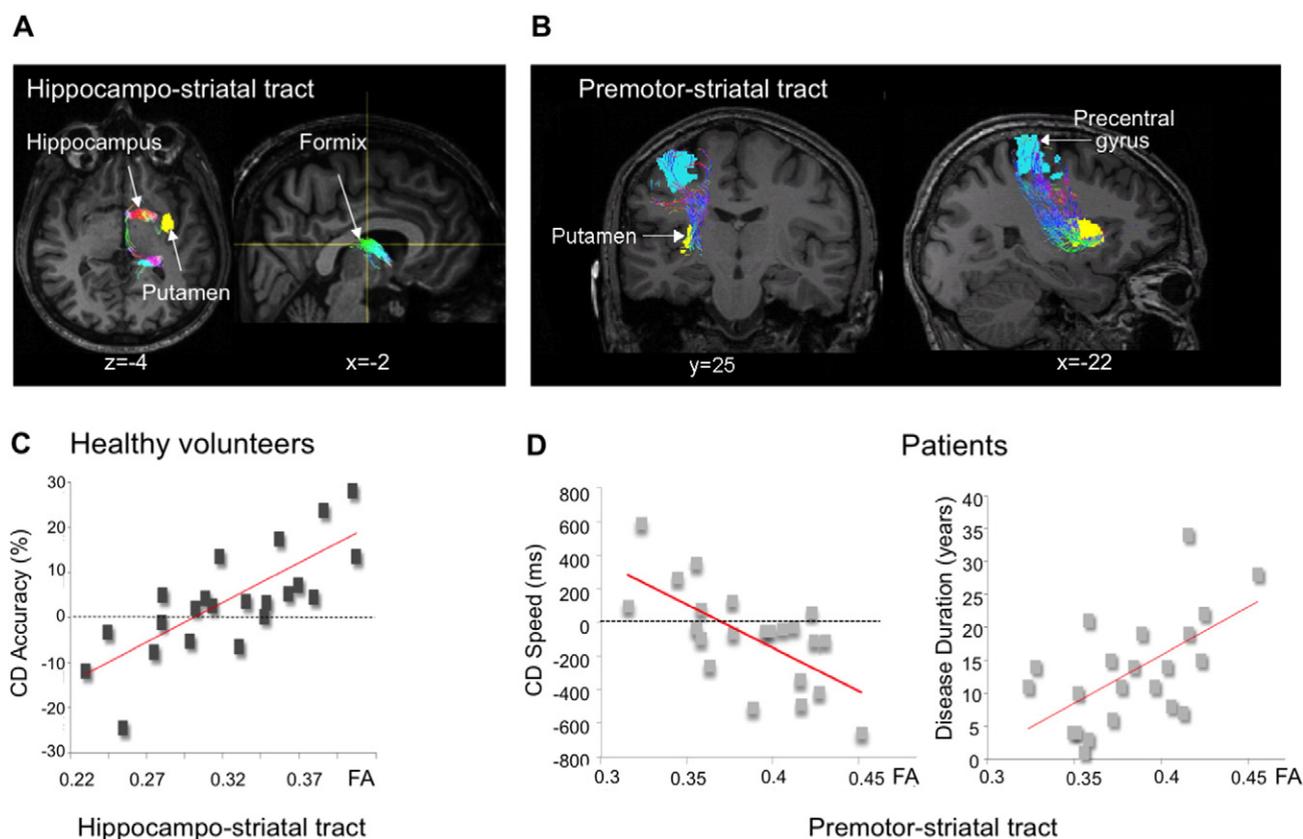


Fig. 5. Structural connectivity of striatal circuits involved in the acquisition of sensorimotor representation. A. Display of the hippocampal–striatal tract in a representative HV. B. Display of the premotor–striatal tract in a representative WC patient. C. Plot of the correlation in HVs between the consolidation-dependent accuracy scores (CD accuracy) and fractional anisotropy along the hippocampal–striatal tract. D. Plots of correlations in WC patients between the CD speed scores (left) and disease duration (right) and fractional anisotropy along the premotor–striatal tract.

cerebellar processing as a compensatory mechanism. This seems unlikely for WC patients because cerebellar input failed to regulate the activity of brain motor circuits in this patient population (Hubsch et al., 2013; Popa et al., 2013b). WC patients had reduced communication between the striatum and the cerebellum in our study, suggesting deficient interactions between the striato-cortical and cerebello-cortical networks. Although there are no direct anatomical connections between the basal ganglia and the cerebellum, indirect connections have been evidenced (Bostan et al., 2013, 2010; Hoshi et al., 2005). In addition, the two networks may interact to tune the primary motor cortex (Kishore et al., 2014; Popa et al., 2013a, 2013b). Lastly in HVs, the interaction between the cerebellar and the striatal networks may allow bridging early to late procedural learning (Censor et al., 2014).

Functional and structural mechanisms supporting the continuous process leading to consolidation of motor performance engaged different striatal networks in WC and in HV. Indeed, the gain in performance on day 2 compared to day 1 correlated with premotor–striatal connectivity in WC, but with hippocampo–striatal connectivity in HV (Figs. 3 and 4). Consolidation of motor skills refers to the stabilization or the gains in performance that occur after practice (Albouy et al., 2008; Debas et al., 2010; Doyon et al., 2009; Karni et al., 1998; Korman et al., 2003; Ungerleider et al., 2002). In HVs, gains in performance observed 24 h after the initial practice were related to functional interactions between the hippocampus and the striatum recorded at the end of motor practice, which is in line with previous results (Albouy et al., 2012, 2008). The neural processes leading to the consolidation of motor performance tested post training may begin during practice and involve cortico-striatal networks (Dayan and Cohen, 2011; Muellbacher et al., 2002). Indeed, transient disruption of the cortico-striatal motor network by transcranial magnetic stimulation alters the recall of motor

skills and fMRI functional connectivity in HVs (Censor et al., 2014). WC patients achieved performance gains similar to HVs, with only a trend for lower speed at recalling the learned sequence after consolidation in the WC. It was already shown that focal hand dystonia patients display a slowness of movement during learning (e.g., Palminteri et al., 2011), which may also be the case for consolidated performance here. In contrast to HVs, WC patients did not rely on hippocampal–striatal connectivity. Instead, consolidation of motor performance in WC patients correlated with functional and structural connectivity between the overactivated premotor cortex and the striatum. This may have implications for the rehabilitation of patients with WC.

WC patients constantly overactivated the lateral premotor areas during the complex sequence. In addition, greater connectivity between the lateral premotor area and the striatum was associated with greater consolidated performance and also longer disease duration. These results suggest that the involvement of premotor–striatal network could be beneficial and compensatory on the short-term during the initial practice session of a new motor skill. The over-recruitment of lateral premotor regions in WC patients was also found during learning in other forms of dystonia (Carbon et al., 2011, 2008; Ghilardi et al., 2003) and during the execution of motor tasks in FHD patients (Ibáñez et al., 1999; Islam et al., 2009; Oga et al., 2002; Peller et al., 2006). Increased activation in premotor areas was commonly interpreted as resulting from reduced inhibition or increased plasticity in the sensorimotor system (Beck et al., 2008; Hallett, 2006; Peller et al., 2006; Quartarone et al., 2003). Increased plasticity may be maladaptive in the long-term, increasing the fatigability of the sensorimotor system with prolonged, intensive practice of highly trained motor skills (Roze et al., 2009). Greater activation of premotor areas during learning may also be due to higher muscular activity during task performance.

This is unlikely because WC patients have task-specific dystonia, i.e., they did not present dystonic contractions during tapping but only during writing.

One limitation of the current study was that we did not study the unaffected limb to determine whether dysfunction of the sensorimotor and hippocampal circuits would also be present. Such dysfunction may be expected in the asymptomatic hemisphere for several reasons. First, the sensory representations of both the pathological and the unaffected hands were altered in the primary sensory cortex in FHD patients (Bleton et al., 2011; Meunier et al., 2001). Second, WC patients tended to develop dystonic symptoms in their non-affected hand over time, suggesting an inner fragility of the sensorimotor system (Beck et al., 2009; Hallett, 2006). Another limitation is that we did not have fMRI recordings during the performance of the complex sequence after 24 h, which could have helped better understand the neural correlates of the recall of sensorimotor representations after consolidation. However, this was not the primary aim of our study. Instead, we focused on how brain processes occurring during motor practice could impact the subsequent consolidation of a motor sequence in WC patients. Finally, differences in force level (not monitored here) to perform the button presses could have influenced posterior striatal activation. However, we did not observe any main effect of Group or any effect of Motor Practice on M1 activation. As force level is closely related to M1 activation level, this suggests that the force level involved during the button presses did not differ between groups and that the over-activation of the sensorimotor striatum was not related to a difference in force production, although this cannot be ascertained.

Conflicts of interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary material for this article can be found online at <http://dx.doi.org/10.1016/j.nicl.2015.04.013>.

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