Published in final edited form as:

Neuroimage. 2012 July 16; 61(4): 823–831. doi:10.1016/j.neuroimage.2012.03.066.

Individuated finger control in focal hand dystonia: an fMRI study

Ryan D Moore, MD^a, Cecile Gallea, PhD^a, Silvina G Horowitz, PhD^a, and Mark Hallett, MD^a

^aHuman Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, NIH, Building 10, Room 7D37, 10 Center Drive, MSC 1428, Bethesda, MD 20892-1428

Abstract

Objectives—To better understand deficient selective motor control in focal hand dystonia by determining changes in striatal activation and connectivity in patients performing individuated finger control.

Methods—Functional imaging with a 3-Tesla magnetic resonance scanner was performed on 18 patients and 17 controls during non-symptom producing tasks requiring right-handed individuated or coupled finger control. A global linear model and psychophysiologic interactions model compared individuated to coupled tasks for patients and controls separately, and the results were submitted to a group analysis. The sensorimotor (posterior) and associative (anterior) putamen were considered as seed regions for the connectivity analysis.

Results—Compared to controls, patients had significant differences in activations and connectivity during individuated compared to coupled tasks: (i) decreased activations in the bilateral postcentral gyri, right associative posterior parietal areas, right cerebellum and left posterior putamen, while activations in the left anterior putamen were not different; (ii) increased connectivity of the left posterior putamen with the left cerebellum and left sensorimotor cortex; (iii) increased connectivity of the left anterior putamen with bilateral supplementary motor areas, the left premotor cortex, and left cerebellum.

Interpretation—Decreased activations in the sensorimotor putamen and cerebellum controlling the affected hand might underlie low levels of surround inhibition during individuated tasks. For identical motor performance in both groups, increased connectivity of sensorimotor and associative striato-cortical circuits in FHD suggests that both affected and unaffected territories of the striatum participate in compensatory processes.

Keywords

motor control; focal hand dystonia; fMRI; striatum; putamen; cerebellum

Introduction

Focal hand dystonia (FHD) is a movement disorder of unknown etiology that is characterized by sustained, involuntary contractions in the muscles of the hand. It is often task specific, as in writer's or musician's cramp, although it may progress to occur with other tasks or even at rest. Electromyographic recordings during tasks that trigger FHD

Corresponding Author: Mark Hallett, MD, Chief, Human Motor Control Section, NINDS, NIH, Building 10, Room 7D37, 10 Center Drive, MSC 1428, Bethesda, MD 20892-1428, 301-496-9526 (phone), 301-480-2286 (fax), hallettm@ninds.nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

symptoms have demonstrated abnormally prolonged muscle firing, co-contraction of agonist and antagonist muscle groups, and overflow activation in inappropriate muscles.(Cohen and Hallett, 1988) Overflow reduces individuated finger control, which requires selective activation and inhibition of neighboring muscle groups.

The motor system is comprised of competing excitatory and inhibitory pathways(Mink, 1996), and motor commands are focused via surround inhibition(Sohn and Hallett, 2004b), a process well known for its role in sensory discrimination. Surround inhibition is the ability to inhibit the cortical representation of the muscles that are not involved in the selective motor task but that are spatially adjacent to (“surrounding”) the representation of the activated muscle. Individual finger movements engage surround inhibition, as the cortical representations of these muscle groups are in close proximity on the primary motor cortex (Penfield W, 1937; Penfield W, 1950). Individuated finger control in complex motor tasks, such as playing a musical instrument, requires that the motor commands be focused and not overflow into neighboring muscles. Thus, while neighboring fingers may not be completely at rest (“inhibited”), surround inhibition is necessary to suppress overflow of the complex motor commands.(Beck et al., 2008; Latash et al., 2002) Thus, impaired individuated finger control in FHD may result from overflow of motor commands due to deficient surround inhibition. Indeed, transcranial magnetic stimulation (TMS) has shown that motor surround inhibition is deficient in FHD(Beck et al., 2008; Chen et al., 1997; Sohn and Hallett, 2004a), especially at low force levels used during fine motor tasks(Beck et al., 2009).

The underlying mechanism of surround inhibition and the primary dysfunction in FHD are not known.(Beck and Hallett). It could originate in disorganization of the primary sensorimotor cortex with an increase of the overlap between the cortical representations of the fingers (Meunier et al., 2001). Short intracortical inhibition (SICI) in the primary motor cortex (M1) is reduced during movement initiation in FHD, leading to speculation that SICI is a contributor to surround inhibition via GABAergic interneurons.(Beck et al., 2008) This is supported by a magnetic resonance spectroscopy study that showed decreased GABA concentration in the contralateral sensorimotor cortex of FHD subjects(Levy and Hallett, 2002), although a later study failed to reproduce these findings(Herath et al.). Both of the aforementioned studies also showed a decrease in GABA concentrations of the lentiform nucleus in FHD subjects (the latter a nonsignificant trend)(Herath et al.; Levy and Hallett, 2002), which suggests dysfunction of the indirect (inhibitory) pathways of the basal ganglia. Decreased output from the putamen in the indirect pathway may result in relative overactivity of the direct (excitatory) pathway with subsequent increase in thalamic output to the motor cortex. This may be a contributor to decreased SICI and impaired motor surround inhibition in FHD. In addition, it has recently been hypothesized that FHD is caused by a deficiency in a specific class of inhibitory interneurons, the location of which could be cortical or striatal.(Hallett) This is supported by a hamster model of paroxysmal dystonia in which there was as loss of striatal parvalbumin-reactive GABAergic interneurons.(Gernert et al., 2000)

Insights into an anatomic basis for FHD come from patients with acquired focal dystonias who were often found to have isolated lesions of the lentiform nucleus.(Brett and Hoare, 1981; Traub and Ridley, 1982) Functional neuroimaging has confirmed dysfunction of the cortico-striato-thalamo-cortical motor loop in FHD, although results have varied due to differences in study design. Increased activations have been identified in the contralateral sensorimotor cortex, basal ganglia, and ipsilateral cerebellum during symptom-provoking tasks(Lerner et al., 2004; Odergren et al., 1998; Preibisch et al., 2001; Pujol et al., 2000), while decreased activations have been found in cortical motor areas and contralateral putamen during motor tasks that do not cause symptoms(Wu et al., 2009). This implies that decreased striatal activations are inherent to FHD, rather than as a result of symptoms

(which may paradoxically increase activations, although this is not consistent in studies provoking mild symptoms(Ibanez et al., 1999)). There is clear evidence that FHD is characterized by abnormalities during asymptomatic periods, including deficient motor surround inhibition(Beck et al., 2008; Beck et al., 2009; Chen et al., 1997; Sohn and Hallett, 2004a), changes in cortical and striatal activations(Ibanez et al., 1999; Lerner et al., 2004; Odergren et al., 1998; Preibisch et al., 2001; Pujol et al., 2000; Wu et al., 2009), and somatotopic disorganization of the contralateral sensory cortex(Bara-Jimenez et al., 1998; Elbert et al., 1998) and putamen(Delmaire et al., 2005).

The current study used fMRI blood-oxygen level dependent (BOLD) signal to detect changes in striatal activity and connectivity in FHD subjects during an individuated finger task requiring selective motor control compared to a coupled finger task requiring synergistic motor control. The motor tasks were designed to avoid triggering dystonic symptoms, and any observed functional changes should be inherent to FHD rather than a result of symptoms. We expected to see abnormal activation patterns in the striatum contralateral to the hand used to perform the task, as well as abnormal connectivity between the striatum and regions of the sensorimotor pathways.

Material and methods

Subjects

Eighteen patients with right-sided FHD (mean age 53.9, range 24-65, 4 females, see Table 1) participated in the study and were recruited from the Human Motor Control Section clinic of the National Institute of Neurological Disorders and Stroke (NINDS). Seventeen age and gender matched healthy volunteers (HVs, mean age 54.1, range 22-66, 4 females) also participated in the study and were recruited from the National Institutes of Health Recruitment and Public Liaison Office (NIH, Bethesda, MD). Patients and HVs were right hand dominant, had no abnormal findings on neurologic exam (except dystonia in patients), were screened to ensure safe magnetic resonance imaging (MRI), and had normal clinical MRI. In addition, patients did not have mirror dystonia or severe dystonia at rest and had not received Botulinum toxin injection within 3 months of the study. All subjects provided informed consent according to procedures approved by the NINDS Institutional Review Board and were compensated for participation.

Task Design

Subjects performed visuo-motor control tasks using the index and middle fingers of their right hand on a computer mouse modified to detect the force applied to its buttons. The modified MRI compatible mouse transmitted the force signal as voltage over a 25-ft fiber optic cable to an instrumentation unit, which connected to a PC via a serial cable. The Lab View graphical user interface displayed the force produced by each finger as the vertical position of a cursor (red for index finger, green for middle finger). Depending on the task, subjects produced variable force on the two mouse buttons to trace a red curve scrolling from right to left on the screen, or produced a constant force to keep the cursor within a narrow green horizontal band. Both the red curve and green band were centered on five Newtons, and the red curve consisted of pseudo-randomized series of points smoothed with a Butterworth filter (4th order). Subjects performed three tasks in a block design: “coupled”, “individuated”, and “rest” (see Fig 1). For the “coupled” task, subjects traced the red curve with both red and green cursors by applying identical force with the index and middle fingers. For the “individuated” task, subjects applied a variable force with the index finger to trace the red curve with the red cursor, while applying a constant force with the middle finger to keep the green cursor within the narrow green band. For the “rest” condition, subjects focused on the red curve but performed no motor task. This allowed intermittent

rest between motor tasks to prevent subjects from becoming fatigued during lengthy fMRI runs. Data from the “rest” condition were not analyzed. After being trained for 40 minutes on the behavioral tasks, subjects underwent five fMRI runs (8 minutes 45 seconds in duration with 1 minute rest between runs). Each of the three conditions lasted 30 seconds, was repeated four times per run, and was followed by 12 seconds of rest. The order of the conditions was randomized for each run and between subjects.

fMRI Acquisition

Imaging was performed using a GE Signa 3T scanner. An 8-channel coil was used. In each of the five functional imaging runs, we acquired 300 whole-brain BOLD echo planar images (EPI) with an acceleration factor (ASSET) of 2 [interleaved, slice thickness, 4 mm; inter-slice gap, 0.3 mm; 33 slices; repetition time (TR), 1.75 s; echo time (TE), 29 ms; matrix, 64×64 ; field of view (FOV), 220 mm; in-plane resolution = $3.5 \times 3.5 \text{ mm}^2$; axial orientation]. Five of the volumes were discarded at the beginning of each run to allow for BOLD equilibrium effects. In addition, a high-resolution T1-weighted magnetization-prepared rapid-acquisition gradient echo sequence of 9 minutes was acquired for each subject for registration purposes (TR, 6.836 s; TE, 2.976 s; FOV, 240; matrix, 256×256 ; slice thickness, 1.3 mm; axial orientation).

Data Analysis

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM5). All functional images were time shifted to correct for slice acquisition timing. Images were realigned to minimize the effect of head motion. Normalization was performed using the mean EPI image registered into Montreal Neurological Institute (MNI) space, and the resulting transformation was applied to all EPI images. Finally, images were smoothed with an 8 mm full-width-half-maximum Gaussian kernel. Statistical analyses were performed in MNI space, and anatomical regions were identified by manual inspection using MNI space utilities.

A global linear model of the BOLD activations displayed voxels with signal changes significantly associated with the model using statistical parametric maps. The model consisted of bi-directional comparisons between individuated and coupled blocks, which were performed separately for each subject. The “coupled” task was used as the control, and the “rest” task was not used in the analysis. Regressors of interest were created by convolving a block function representing task onset and duration with a canonical hemodynamic response function. The group analysis consisted of (i) one sample t-tests to look at activation differences between individuated and coupled condition within each group; (ii) two sample t-test to look at activation differences between groups. The hypothesis included the putamen, which has distinct functional and anatomical limbic, associative and sensorimotor territories (Draganski et al., 2008; Haber, 2003). Dystonic patients have somatotopic disorganization in the contralateral putamen which may be the result of abnormal corticostriatal projections. (Delmaire et al., 2005) In healthy controls, activity in the associative part and the sensorimotor part of the putamen has different time course evolution during the performance of motor tasks (Lehericy et al., 2004). Therefore, to see the differences in activation for individuated versus coupled activity within the contralateral putaminal territories, we performed a region of interest (ROI) using a small volume correction (SVC) analysis (threshold of $p < 0.05$ without correcting for multiple comparisons, with 20 voxels as an extent threshold to look at consistent activation within functional territories). The mask for the left putamen was chosen a priori in the anatomical automatic labeling marsbar toolbox. (Tzourio-Mazoyer et al., 2002)

A psychophysiological interactions (PPI) model (Friston et al., 1997; Gitelman et al., 2003) displayed task-dependent changes in functional connectivity between seed volumes of interest (VOIs) and the whole brain for each subject. VOIs were anatomically selected in the contralateral (left) rostroventromedial (anterior) and caudodorsolateral (posterior) putamen according to the parcellation described by Haber (2003) and Draganski and colleagues (2008), representing the associative and sensorimotor territories, respectively. (Draganski et al., 2008; Haber, 2003) Inter-regional covariation of the time series was determined for comparisons between individuated and coupled blocks, where the coupled blocks were used as the control.

The activation and functional connectivity analyses at the individual level were submitted to a group analysis (paired t-test) comparing individuated vs coupled tasks (bi-directional) for patients vs HVs. Results were FDR-corrected at $p < 0.05$, except where otherwise specified (ROI analyses). Accuracy of motor output and degree of individuation were used as covariates to remove the effect of inter-subject variability of the behavioral responses on brain activations. Degree of individuation was measured as the correlation coefficient between the performance of the index and the middle finger. A low correlation coefficient indicated more individuation. Accuracy of the task was measured by correlating the finger performance with the target red line. A high correlation coefficient indicated high accuracy. Both computations were performed in Matlab (using `corrcoef` function).

Finally, to test whether the type of dystonia (writer's cramp (WC), musician's cramp (MC)) had an effect of the activation level and functional connectivity during the tasks, we separated the patient population in two groups (WC=8, MC=6), excluding the patients with both types of dystonia ($n=4$). For the activation analysis, we considered a 2 by 2 factorial design with the (between-group) factor GROUP (2 levels: WC, MC) and the (within-subject) factor condition (2 levels: Individuated, Coupled). The influence of the number of subjects in each group was taken into account in the contrast weights for main effects following the method described in the SPM8 manual (2011). The age was included as a covariate of non-interest (mean age WC = 49.25 ± 11.08 , mean age MC = 58.3 ± 5.46). For the functional connectivity analysis, we considered the same 2 by 2 factorial design with the (between-group) factor GROUP (2 levels: WC, MC) and the (within-subject) factor ROI (2 levels: posterior putamen, anterior putamen). Results were considered significant with a threshold at $p < 0.05$ FDR-corrected for multiple comparisons.

Results

Behavioral Results

FHD subjects and controls had no significant difference in accuracy of 2nd digit ($p=0.39$) or 3rd digit ($p=0.47$), or in their ability to couple ($p=0.73$) and individuate ($p=0.22$) their 2nd and 3rd digits, as calculated using a 2 sample t-test (see Table 2). Similarly, there was no difference between the subgroups of FHD patients in accuracy of 2nd digit ($p=0.85$) or 3rd digit ($p=0.87$), or in ability to couple ($p=0.53$) and individuate ($p=0.78$) their 2nd and 3rd digits. None of the subjects reported experiencing dystonic posture during the tasks.

Activation maps

Within group analysis: Individuated versus Coupled—Activation maps are displayed in Figure 2 and the anatomical localization of the significant clusters of activation are displayed in Table 3. When compared to coupled tasks, HVs performing individuated tasks had decreased activations in regions of the sensorimotor network: bilateral thalamic nuclei, substantia nigra, bilateral supplementary motor area, and bilateral cingulate motor area (BA 24) (Fig 2A). Other areas involved in visual processing and attention showed the

same pattern of decreased activations during the individuated task: bilateral medial visual areas (lingual gyrus) and the precuneus. FHD subjects had decreased activations in the left primary sensorimotor cortex during individuated tasks compared to coupled tasks, but additionally had widespread decreased activations in other sensorimotor areas, including right primary sensory cortex (S1), the right intraparietal sulcus, bilateral supplementary motor area (SMA), bilateral cerebellum, bilateral thalamus, bilateral globus pallidus, and left posterior putamen (Fig 2B). As with HVs, other areas involved in visual processing and attention showed the same pattern of decreased activations during the individuated task: bilateral medial visual areas (lingual gyrus) and the precuneus.

Between group analysis: Individuated versus Coupled—When compared with HVs, FHD subjects had significantly decreased activations in the S1 and associative parietal areas (more on the right than on the left), the right sensorimotor territory of the cerebellum (lobule 6), and the dentate nucleus, as well as in the left posterior putamen ($p < 0.05$ with 20 voxels as extent threshold, ROI analysis), during individuated tasks compared to coupled tasks (Fig 2C). No significant increase in activations was seen for individuated vs coupled tasks.

Connectivity maps

In the HV group, functional connectivity between the left posterior putamen and the whole brain did not differ between the individuated tasks and the coupled tasks at the chosen threshold of significance ($p < 0.05$). In the FHD subjects, the left posterior putamen had increased connectivity with the left sensorimotor territory of the cerebellum (lobule 6), and left lateral and medial visual areas (BA 18,19). When compared to HVs, FHD subjects had significantly increased connectivity between the left posterior putamen and the left cerebellum and left dentate nucleus, as well as left primary sensorimotor cortex ($p < 0.05$ with 20 voxels as extent threshold, ROI analysis), during individuated tasks compared to coupled tasks.

In the HV group, the left anterior putamen had increased connectivity with lateral and medial visual areas bilaterally (BA 17,18,19), during individuated tasks compared to coupled tasks (see Fig 4 and Table 5). In FHD subjects, the left anterior putamen had increased connectivity with the right S1 and associative parietal areas (BA 5,7), M1 and premotor areas, left thalamus, bilateral posterior cingulate and bilateral visual areas (BA 18,19) during individuated tasks compared to coupled tasks. When compared to HVs, FHD subjects had increased connectivity between the left anterior putamen and areas of the sensorimotor network during individuated tasks compared to coupled tasks: bilateral supplementary motor area, bilateral cingulate motor area (BA 24), the left primary motor cortex, the left PMC, and the left cerebellum (lobule 6, with an extension to the visual areas (BA 18,19)). No significant decrease in connectivity was seen for individuated vs coupled tasks in any of these models.

Factorial Analysis: effect of the type of dystonia—For the effect of the type of dystonia on the activation level during the tasks, there was no significant main effect of group or condition ($p > 0.05$ FDR), meaning that WC and MC activated similar sensorimotor networks for the individuated and the coupled conditions. For the effect of the type of dystonia on the functional connectivity of the putamen, there was no significant main effect of the group or ROI ($p > 0.05$ FDR), meaning that the posterior and anterior putamen interacted with similar networks during the individuated task in both groups. It has to be noted that the low number of subjects in each group reduced the statistical power of the analysis.

Discussion

FHD subjects performing individuated tasks compared to coupled tasks had widespread decreased activations in sensorimotor regions that were not seen in HVs. Despite decreased activity in the left posterior (sensorimotor) putamen, FHD subjects had increased connectivity between the left posterior putamen and left-sided cortical and cerebellar motor regions. Furthermore, the left anterior (associative) putamen, which did not show abnormal activation patterns, showed increased connectivity with cortical and cerebellar areas involved in motor planning (a known function of the anterior putamen (Gerardin et al., 2004)) during tasks requiring individuated finger control when compared to coupled tasks. Considering that the task did not provoke dystonic symptoms and was performed with similar accuracy by the two groups, it is likely that these differences reflect intrinsic pathologic changes or compensatory mechanisms rather than symptoms or behavioral differences.

These changes are specific to individuated finger control in FHD, and by extension may give insight into the underlying deficits in motor inhibition. The individuated task requires selective focusing of a complex motor command on the tracking finger, while the neighboring finger performs a tonic movement. Thus, compared to the synergistic control task, the individuated task requires surround inhibition of the complex motor command to prevent overflow into the neighboring tonically contracted finger. The motor command during non-synergetic versus synergetic finger tasks involves sophisticated patterns of excitatory and inhibitory signals to the finger muscles, and active suppression of the innate synergetic motor pattern (Loffe, 1992; Schieber, 1996). While this is not surround inhibition in a strict sense (complete inhibition of neighboring finger), the differences between individuated and synergistic movements provide insight into deficient motor surround inhibition in FHD.

Our findings agree with a previous study that showed decreased sensorimotor activations in FHD subjects performing simple motor tasks that did not provoke symptoms (Wu et al., 2009). However, that study compared finger tapping directly between patients and controls, while ours compared individuated to coupled movements within each group separately, looking for different changes in the two groups. In addition to the similar findings of decreased S1, posterior parietal cortex, striatal, and cerebellar activations, their study found decreased activations in M1 and SMA. Given that finger tapping requires individuated finger control, the overlapping subset of decreased activations in S1, striatum, and cerebellum are likely specific to finger individuation, while the additional findings of decreased activations in cortical motor areas may be non-specific changes seen with hand movement in FHD.

Increased activations in the basal ganglia, sensorimotor cortex, sensorimotor association areas, and cerebellum have been identified in FHD during symptom-provoking tasks (Lerner et al., 2004; Odergren et al., 1998; Preibisch et al., 2001; Pujol et al., 2000), although one study found decreased PMC activity during mild symptoms (Ibanez et al., 1999). FHD seems to be characterized by overactivity of sensorimotor regions during dystonic posturing and underactivity during asymptomatic fine motor control. The areas that are specifically underactive during individuated finger control are important modulators of motor cortex activity and may contribute to motor surround inhibition. For instance, intracortical loops connecting S1 and M1 could play an important role in regulating cortical motor activity during sensorimotor integration tasks (Catani et al. 2011). The contralateral posterior putamen is involved in movement execution (Gerardin et al., 2004) and is a component of the direct and indirect pathways of the basal ganglia that compete to promote or inhibit movement, respectively (Mink, 1996). Underactivity of the indirect pathway may decrease

individuated finger control by allowing a relative overactivity of the direct pathway, and deficiency of GABAergic interneurons in the striatum is one possible mechanism for decreased surround inhibition in FHD. (Hallett) The cerebellum is also involved in motor coordination and individuated finger control (Debaere et al., 2004; Ehrsson et al., 2002) and has been shown to modulate SICI in HVs (Daskalakis et al., 2004). TMS has recently been used to demonstrate absence of cerebellar modulation of SICI in FHD compared to HVs (Brighina et al., 2009), suggesting that dysfunction of the cerebellum could be a source of decreased surround inhibition. In light of recent studies showing direct disynaptic connections between the striatum and cerebellum in monkeys (Bostan et al., 2010; Hoshi et al., 2005), it is not clear whether FHD results from primary cerebellar dysfunction, abnormal basal ganglia output via striato-cerebellar pathways, or secondary to a structural change affecting multiple areas of the brain. Somatotopic disorganization has been shown in contralateral S1 (Bara-Jimenez et al., 1998; Elbert et al., 1998) and putamen (Delmaire et al., 2005; Meunier et al., 2001), and gray matter decrease has been found in contralateral primary sensorimotor cortex, bilateral thalamus, and cerebellum (Delmaire et al., 2007).

While decreased sensorimotor activations may be a primary deficit in FHD, the effect of learning and repetition must be considered. Decreased activations in the cerebellum (Doyon et al., 2002; Lehericy et al., 2005) and associative putamen (Lehericy et al., 2005) are known to occur following extensive repetition of movements, and there is an accompanying increase in activity in the sensorimotor putamen (Lehericy et al., 2005) and cortical motor areas (pre-SMA, SMA proper, premotor and superior parietal cortices) (Jueptner et al., 1997; Lehericy et al., 2005). It is unlikely that the observed decrease in cerebellar activations are due to learning, as the decrease was specific to individuated finger movements in FHD, which should be more difficult to learn than coupled movements given the same training time. Additionally, decreased cerebellar activations were not seen in HVs. Finally, posterior sensorimotor striatal activations decreased in FHD subjects during individuated finger control, rather than increase as is typically seen with learning (Lehericy et al., 2005).

FHD subjects had increased connectivity in the striato-cerebellar and striato-cortical networks, which may represent a compensatory change rather than a primary dysfunction in FHD. Decreased connectivity in these networks is observed in movement disorders such as Parkinson's disease, where connectivity is negatively correlated with the severity of the motor dysfunction. (Wu et al.) Parkinson's patients typically have worse performance or require longer training periods than HVs to achieve comparable performance, whereas in our study FHD subjects and controls trained for identical times and had similar performance. It appears that the increase in connectivity between left putamen, left cerebellum, and cortical sensorimotor areas are compensatory for the dysfunction of the putamen and right cerebellum during individuated finger control, allowing for normal performance during non-symptom-provoking tasks. The basal ganglia and cerebellum, have been shown to decrease in activity and increase in connectivity during automated tasks in HVs. (Wu et al., 2008; Wu et al., 2004) It is possible that FHD patients had decreased activations and increased connectivity in these regions due to compensatory automatization for deficient individuated finger control, while coupled movements required no compensation for accurate performance.

The anterior associative part of the putamen had different connectivity patterns in patients and controls. Patients recruited more interactions with non primary motor areas (SMA, CMA, PM) compared to controls. The anterior putamen receives anatomical projections from the premotor cortex and prefrontal areas involved in attention to action and multimodal sensorimotor integration (Draganski et al., 2008; Haber, 2003; Jueptner and Weiller, 1998; Lehericy et al., 2004; Rowe et al., 2002). The anterior putamen and visual areas involved in visuomotor transformation (Vaillancourt et al., 2003) were equally functionally connected in

patients and healthy controls. Similarly, connectivity between the associative putamen and the precuneus observed in both patients and healthy controls suggests that FHD patients did not require more connectivity in the attention network to compensate for basal ganglia dysfunction. In other words, the difference of the anterior putamen connectivity observed between patients and healthy controls was isolated in sensorimotor areas specifically recruited during the performance of individuated finger movements like SMA, M1, the cerebellum and the ipsilateral putamen. Thus, abnormal functional connectivity observed in FHD patients might not be confined to the sensorimotor territory of the putamen, like it is the case for the structural connectivity deficits observed in diffusion tensor imaging studies (Delmaire et al., 2005).

Limitations

The patient group had a large number of musicians (9/18), which may have confounded the results. Musicians (without FHD) have superior individuated finger control, are more accurate at reaching desired force levels, and show less enslaving than non-musicians. (Slobounov et al., 2002) This is thought to be due to expanded cortical sensorimotor representation, a process that may well become pathologic in FHD (Bara-Jimenez et al., 1998) and is unlikely to continue contributing to superior individuated control. During tasks requiring sensorimotor synchronization (index finger tapping to auditory rhythm), musicians had increased connectivity between the thalamus and PMC compared to controls. (Krause et al.) However, this was not shown to be unique to individuated finger movements. Thus, it is possible, but unlikely, that increased connectivity during individuated tasks compared to coupled tasks in FHD patients compared to healthy volunteers was due to the high percentage of musicians in the FHD group. Likewise, it is also possible that decreased activations in FHD patients compared to healthy volunteers is secondary to increased efforts required by non-musician healthy volunteers to perform individuated tasks.

Conclusions

Decreased activations in the contralateral posterior putamen and ipsilateral cerebellum in FHD during individuated tasks compared to coupled tasks suggest that these areas are involved in deficient selective motor control. By extension, these areas may also be involved in deficient motor surround. The increased connectivity between striatum and motor areas during individuated tasks compared to coupled tasks may be compensatory in nature. Further studies with a larger population of patients are needed to investigate the possible difference in neurologic dysfunctions between writer's and musician's cramps.

References

- Bara-Jimenez W, Catalan MJ, Hallett M, Gerloff C. Abnormal somatosensory homunculus in dystonia of the hand. *Ann Neurol*. 1998; 44:828–831. [PubMed: 9818942]
- Beck S, Hallett M. Surround inhibition in the motor system. *Exp Brain Res*. 2011; 210:165–172. [PubMed: 21424259]
- Beck S, Richardson SP, Shamim EA, Dang N, Schubert M, Hallett M. Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. *J Neurosci*. 2008; 28:10363–10369. [PubMed: 18842895]
- Beck S, Schubert M, Richardson SP, Hallett M. Surround inhibition depends on the force exerted and is abnormal in focal hand dystonia. *J Appl Physiol*. 2009; 107:1513–1518. [PubMed: 19713426]
- Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. *Proc Natl Acad Sci U S A*. 2010; 107:8452–8456. [PubMed: 20404184]
- Brett EM, Hoare RD. Progressive hemi-dystonia due to focal basal ganglia lesion after mild head trauma. *J Neurol Neurosurg Psychiatry*. 1981; 44:460. [PubMed: 7264700]

- Brighina F, Romano M, Giglia G, Saia V, Puma A, Giglia F, Fierro B. Effects of cerebellar TMS on motor cortex of patients with focal dystonia: a preliminary report. *Exp Brain Res*. 2009; 192:651–656. [PubMed: 18815775]
- Chen R, Wassermann EM, Canos M, Hallett M. Impaired inhibition in writer's cramp during voluntary muscle activation. *Neurology*. 1997; 49:1054–1059. [PubMed: 9339689]
- Cohen LG, Hallett M. Hand cramps: clinical features and electromyographic patterns in a focal dystonia. *Neurology*. 1988; 38:1005–1012. [PubMed: 3386815]
- Daskalakis ZJ, Paradiso GO, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. Exploring the connectivity between the cerebellum and motor cortex in humans. *J Physiol*. 2004; 557:689–700. [PubMed: 15047772]
- Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Cerebellar and premotor function in bimanual coordination: parametric neural responses to spatiotemporal complexity and cycling frequency. *Neuroimage*. 2004; 21:1416–1427. [PubMed: 15050567]
- Delmaire C, Krainik A, Tezenas du Montcel S, Gerardin E, Meunier S, Mangin JF, Sangla S, Garnero L, Vidailhet M, Lehericy S. Disorganized somatotopy in the putamen of patients with focal hand dystonia. *Neurology*. 2005; 64:1391–1396. [PubMed: 15851729]
- Delmaire C, Vidailhet M, Elbaz A, Bourdain F, Bleton JP, Sangla S, Meunier S, Terrier A, Lehericy S. Structural abnormalities in the cerebellum and sensorimotor circuit in writer's cramp. *Neurology*. 2007; 69:376–380. [PubMed: 17646630]
- Doyon J, Song AW, Karni A, Lalonde F, Adams MM, Ungerleider LG. Experience-dependent changes in cerebellar contributions to motor sequence learning. *Proc Natl Acad Sci U S A*. 2002; 99:1017–1022. [PubMed: 11805340]
- Draganski B, Kherif F, Kloppel S, Cook PA, Alexander DC, Parker GJ, Deichmann R, Ashburner J, Frackowiak RS. Evidence for segregated and integrative connectivity patterns in the human Basal Ganglia. *J Neurosci*. 2008; 28:7143–7152. [PubMed: 18614684]
- Ehrsson HH, Kuhtz-Buschbeck JP, Forssberg H. Brain regions controlling nonsynergistic versus synergistic movement of the digits: a functional magnetic resonance imaging study. *J Neurosci*. 2002; 22:5074–5080. [PubMed: 12077202]
- Elbert T, Candia V, Altenmüller E, Rau H, Sterr A, Rockstroh B, Pantev C, Taub E. Alteration of digital representations in somatosensory cortex in focal hand dystonia. *Neuroreport*. 1998; 9:3571–3575. [PubMed: 9858362]
- Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage*. 1997; 6:218–229. [PubMed: 9344826]
- Gerardin E, Pochon JB, Poline JB, Tremblay L, Van de Moortele PF, Levy R, Dubois B, Le Bihan D, Lehericy S. Distinct striatal regions support movement selection, preparation and execution. *Neuroreport*. 2004; 15:2327–2331. [PubMed: 15640749]
- Gernert M, Hamann M, Bennay M, Loscher W, Richter A. Deficit of striatal parvalbumin-reactive GABAergic interneurons and decreased basal ganglia output in a genetic rodent model of idiopathic paroxysmal dystonia. *J Neurosci*. 2000; 20:7052–7058. [PubMed: 10995851]
- Gitelman DR, Penny WD, Ashburner J, Friston KJ. Modeling regional and psychophysiological interactions in fMRI: the importance of hemodynamic deconvolution. *Neuroimage*. 2003; 19:200–207. [PubMed: 12781739]
- Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat*. 2003; 26:317–330. [PubMed: 14729134]
- Hallett M. Neurophysiology of dystonia: The role of inhibition. *Neurobiol Dis*. 2011; 42:177–184. [PubMed: 20817092]
- Herath P, Gallea C, van der Veen JW, Horovitz SG, Hallett M. In vivo neurochemistry of primary focal hand dystonia: a magnetic resonance spectroscopic neurometabolite profiling study at 3T. *Mov Disord*. 2010; 25:2800–2808. [PubMed: 20979122]
- Hoshi E, Tremblay L, Feger J, Carras PL, Strick PL. The cerebellum communicates with the basal ganglia. *Nat Neurosci*. 2005; 8:1491–1493. [PubMed: 16205719]
- Ibanez V, Sadato N, Karp B, Deiber MP, Hallett M. Deficient activation of the motor cortical network in patients with writer's cramp. *Neurology*. 1999; 53:96–105. [PubMed: 10408543]

- Jueptner M, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning II. Subcortical structures and learning by trial and error. *J Neurophysiol.* 1997; 77:1325–1337. [PubMed: 9084600]
- Jueptner M, Weiller C. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. *Brain.* 1998; 121(Pt 8):1437–1449. [PubMed: 9712006]
- Krause V, Schnitzler A, Pollok B. Functional network interactions during sensorimotor synchronization in musicians and non-musicians. *Neuroimage.* 2010; 52:245–251. [PubMed: 20363337]
- Lataash ML, Li S, Danion F, Zatsiorsky VM. Central mechanisms of finger interaction during one- and two-hand force production at distal and proximal phalanges. *Brain Res.* 2002; 924:198–208. [PubMed: 11750905]
- Lehericy S, Benali H, Van de Moortele PF, Pelegrini-Issac M, Waechter T, Ugurbil K, Doyon J. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. *Proc Natl Acad Sci U S A.* 2005; 102:12566–12571. [PubMed: 16107540]
- Lehericy S, Ducros M, Van de Moortele PF, Francois C, Thivard L, Poupon C, Swindale N, Ugurbil K, Kim DS. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann Neurol.* 2004; 55:522–529. [PubMed: 15048891]
- Lerner A, Shill H, Hanakawa T, Bushara K, Goldfine A, Hallett M. Regional cerebral blood flow correlates of the severity of writer's cramp symptoms. *Neuroimage.* 2004; 21:904–913. [PubMed: 15006657]
- Levy LM, Hallett M. Impaired brain GABA in focal dystonia. *Ann Neurol.* 2002; 51:93–101. [PubMed: 11782988]
- Loffe ME. Mechanisms of motoric learning. *Neurosci Behav Physiol.* 1992; 22:481–494. [PubMed: 1480259]
- Meunier S, Garnero L, Ducorps A, Mazieres L, Lehericy S, du Montcel ST, Renault B, Vidailhet M. Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization. *Ann Neurol.* 2001; 50:521–527. [PubMed: 11601503]
- Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. *Prog Neurobiol.* 1996; 50:381–425. [PubMed: 9004351]
- Odergren T, Stone-Elander S, Ingvar M. Cerebral and cerebellar activation in correlation to the action-induced dystonia in writer's cramp. *Mov Disord.* 1998; 13:497–508. [PubMed: 9613744]
- Penfield W, B E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain.* 1937; 60:389–433.
- Penfield, W.; R, T. A clinical study of localization of function. Macmillan; New York: 1950. The cerebral cortex of man.
- Preibisch C, Berg D, Hofmann E, Solymosi L, Naumann M. Cerebral activation patterns in patients with writer's cramp: a functional magnetic resonance imaging study. *J Neurol.* 2001; 248:10–17. [PubMed: 11266013]
- Pujol J, Roset-Llobet J, Rosines-Cubells D, Deus J, Narberhaus B, Valls-Sole J, Capdevila A, Pascual-Leone A. Brain cortical activation during guitar-induced hand dystonia studied by functional MRI. *Neuroimage.* 2000; 12:257–267. [PubMed: 10944408]
- Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. *Brain.* 2002; 125:276–289. [PubMed: 11844728]
- Schieber, M. Individuated finger movements: rejecting the labeled-line hypothesis. In: Wing, AM.; Flanagan, HP., JR, editors. *Hand and brain.* Academic; New York: 1996. p. 81-98.
- Slobounov S, Chiang H, Johnston J, Ray W. Modulated cortical control of individual fingers in experienced musicians: an EEG study. *Electroencephalographic study.* *Clin Neurophysiol.* 2002; 113:2013–2024. [PubMed: 12464342]
- Sohn YH, Hallett M. Disturbed surround inhibition in focal hand dystonia. *Ann Neurol.* 2004a; 56:595–599. [PubMed: 15455393]
- Sohn YH, Hallett M. Surround inhibition in human motor system. *Exp Brain Res.* 2004b; 158:397–404. [PubMed: 15146307]

- Traub M, Ridley A. Focal dystonia in association with cerebral infarction. *J Neurol Neurosurg Psychiatry*. 1982; 45:1073–1074. [PubMed: 7175538]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002; 15:273–289. [PubMed: 11771995]
- Vaillancourt DE, Thulborn KR, Corcos DM. Neural basis for the processes that underlie visually guided and internally guided force control in humans. *J Neurophysiol*. 2003; 90:3330–3340. [PubMed: 12840082]
- Wu CC, Fairhall SL, McNair NA, Hamm JP, Kirk IJ, Cunningham R, Anderson T, Lim VK. Impaired sensorimotor integration in focal hand dystonia patients in the absence of symptoms. *J Neurol Neurosurg Psychiatry*. 2009
- Wu T, Chan P, Hallett M. Modifications of the interactions in the motor networks when a movement becomes automatic. *J Physiol*. 2008; 586:4295–4304. [PubMed: 18617569]
- Wu T, Kansaku K, Hallett M. How self-initiated memorized movements become automatic: a functional MRI study. *J Neurophysiol*. 2004; 91:1690–1698. [PubMed: 14645385]
- Wu T, Wang L, Hallett M, Chen Y, Li K, Chan P. Effective connectivity of brain networks during self-initiated movement in Parkinson's disease. *Neuroimage*. 2011; 55:204–215. [PubMed: 21126588]

Abbreviations

FHD	focal hand dystonia
TMS	Transcranial magnetic stimulation
SICI	Short intracortical inhibition

Figure 1.

Behavioral task. Using a stationary, force sensitive mouse, the right index finger controlled the vertical position of the red cursor, and the right middle finger controlled the vertical position of the green cursor. A) Coupled task: both index and middle fingers produced identical forces to synchronously move the red and green cursors along the red curve. B) Individuated task: the index finger produced a variable force to trace the red curve with the red cursor, while the middle finger produced a constant force to keep the green cursor within the green band. C) Rest: the subject focused on the middle of the screen, without producing any force on the mouse.

Figure 2.

Global linear model showing decreased activations during individuated tasks compared to coupled tasks for A) HVs, B) FHD, and C) FHD compared to HVs. All results are displayed on a glass brain at $p < 0.05$ FDR corrected. Lower case letters refer to the anatomical localization of significantly activated clusters labeled in Table 3. The red framed portion indicates the results for the ROI analysis.

Figure 3. PPI analysis showing increased connectivity with the left posterior putamen during individuated tasks compared to coupled tasks for A) FHD, and B) FHD compared to HVs. There was no significant difference between tasks for HVs. All results are displayed on a glass brain at $p < 0.05$ FDR corrected. Lower case letters refer to the anatomical localization of significantly activated clusters labeled in Table 4. The red framed portion indicates the results for the ROI analysis.

Figure 4. PPI analysis showing increased connectivity with the left anterior putamen during individuated tasks compared to coupled tasks for A) HVs, B) FHD, and C) FHD compared to HVs. All results are displayed on a glass brain at $p < 0.05$ FDR corrected. Lower case letters refer to the anatomical localization of significantly activated clusters labeled in Table 5.

Table 1

Clinical characteristics of patients.

Subject	Age	Sex	Form of Dystonia	Disease Duration	Treatment
S01	56	M	WC	15	BTX FC
S02	59	M	MC	12	BTX FC
S03	57	M	MC and WC	22	None
S04	57	M	Keyboard mouse	15	None
S05	22	F	WC	2	BTX FC
S06	66	M	MC	18	None
S07	58	M	MC	5	BTX FC
S08	58	M	MC and WC	15	None
S09	58	M	MC	9	None
S10	51	F	WC	4	BTX FC
S11	60	F	WC	5	BTX FC
S12	50	F	WC	13	BTX FC
S13	49	M	MC	15	BTX FC
S14	60	M	MC	8	BTX FC
S15	51	M	WC	15	None
S16	65	M	MC and WC	41	None
S17	47	M	WC	20	None
S18	29	M	MC and WC	5	None

Form of dystonia: MC: musician's cramp; WC: writer's cramp; **Treatment:** None: no Botulinum toxin injection for more than 1 year; BTX FC: full cycle (at least 3 month since last injection to the scan time)

Behavioral data: accuracy and degree of coupling as measured by correlating force output with the task curve and between the 2nd and 3rd digits.

Table 2

	Main Analysis		FHD Sub-analysis			
	FHD mean(SD)	HV mean(SD)	p-value	MC mean(SD)	WC mean(SD)	p-value
2 nd digit accuracy (vs curve)	.69 (.15)	.73 (.12)	0.39	.68 (.12)	.67 (.15)	0.85
3 rd digit accuracy (vs curve)	.72 (.13)	.75 (.11)	0.47	.72 (.16)	.71 (.18)	0.87
Coupling coef (2 nd vs 3 rd)	.68 (.19)	.70 (.15)	0.73	.71 (.12)	.68 (.13)	0.53
Individuation coef (2 nd vs 3 rd)	.24 (.17)	.18 (.10)	0.22	.30 (.22)	.28 (.15)	0.78

coef=coefficient; MC = Musician's Cramp; WC = Writer's Cramp; SD = standard deviation

Table 3

Anatomical localization of clusters for the activation analysis. Lower case letters in the first column refer to the anatomical views displayed in Figure 2A, B and C.

Anatomical Regions	MNI Coordinates of local maxima (x,y,z)	T-score of local max	Volume (# voxels)	p value (FDR)
A) HV: Individuated<Coupled				
a BL Lingual Gyrus(BA 19, 18)	4,-38,-2	8.09	1129	0.0001
CE: Cuneus and Precuneus (BA 31, 7), Posterior Cingulate (BA 29,23)	0,-70,26	5.04		
CE: Inferior part of Lingual Gyrus(BA 19)	-6,-64,0	5.02		
b R and L Thalamus (ventral lateral nucleus), Sub-thalamic nucleus, Substantia Nigra	12,-8,-6	7.8	903	0.001
CE: R Substantia Nigra	16,-24,-16	6.4		
CE: R Parahippocampal Gyrus	22,-6,18	5.46		
c BL Medial Superior Frontal Gyrus (BA 9, 10)	2,46,26	6.1	250	0.041
CE: L Anterior Cingulate (BA 32)	-2,44,14	5.39		
CE: R Anterior Cingulate (BA 32)	6,46,10	5.1		
d L Supplementary Motor Area (BA 6)	-4,-18,48	4.96	305	0.019
CE: Cingulate Gyrus (BA 24), L Paracentral Lobule (BA 5,7), Precuneus (BA 31)	-6,-28,52	4.85		
CE: R Supplementary Motor Area (BA 6)	8,-16,56	4.52		
B) FHD: Individuated<Coupled				
a L Cerebellum (lobule 4, 5)	-6,-60,-6	7	9134	0.0001
CE: R and L Precuneus (BA 31, 7), Posterior Cingulate (BA 29,23), Lingual Gyrus (BA 18, 19)	16,-52,28	6.61		
CE: R Cerebellum (lobule 4, 5), BL Vermis	10,-58,-18	6.26		
b L Precentral Gyrus (BA 4)	-30,-22,54	5.69	1045	0.0001
CE: L Postcentral Gyrus (BA 1,2,3)	-36,-38,70	5.98		
CE: L Postcentral Gyrus, Inferior Parietal Lobule (BA 40)	-38,-26,48	4.76		
c R Intra Parietal Sulcus	30,-42,46	5.54	1981	0.0001
CE: R Superior Parietal Lobule (BA 7)	40,-50,66	5.5		
CE: R Paracentral Lobule (BA 5)	6,-90,68	5.18		
d L Putamen	-28,-8,6	5.32	881	0.001
CE: L Thalamus (Ventral Lateral nucleus), L Globus Pallidus (medial and lateral)	-12,-16,8	5.11		
CE: L Substantia Nigra	-6,-18,-12	4.54		
e R Globus Pallidus (lateral)	18,-4,2	5.23	574	0.006
CE: R Thalamus (Ventral Lateral Nucleus)	26,-14,2	3.79		
C) FHD<HV				
a R Postcentral Gyrus (BA 1,2,3)	18,-36,80	5.03	2800	0.002
CE: R Postcentral Gyrus (BA 1,2,3), Superior and Inferior Parietal Lobule (BA 7,40)	28,-40,66	3.76		
CE: BL Paracentral Lobule (BA 5), L Postcentral Gyrus (BA 1,2,3)	-38,-34,66	3.65		
b R Cerebellum (lobule 6)	28,-50,-26	3.98	1045	0.046

Anatomical Regions	MNI Coordinates of local maxima (x,y,z)	T-score of local max	Volume (# voxels)	p value (FDR)
<i>CE; R Dentate</i>	<i>16,-52,-28</i>	<i>3.26</i>		
c ROI analysis: L Putamen	-28,4,6	3.2	20	na

BA = Brodmann area; CE = cluster extension; BL = bilateral, L = left, R = right. ROI analysis: mask over bilateral lentiform nuclei, uncorrected threshold at $p < 0.05$ with 20 voxels as extent threshold.

Table 4

Anatomical localization of clusters for the functional connectivity analysis of the left posterior putamen. Lower case letters of the first column refer to anatomical views displayed in Figure 3A and B.

Anatomical Regions	MNI Coordinates of local maxima (x,y,z)	T-score of local max	Volume (# voxels)	p value (FDR)
A) FHD: Individuated>Coupled				
a L Lingual Gyrus(BA 19, 18)	-24,-78,-16	6.96	1129	0.005
CE: L Lingual Gyrus (BA 19)	-18,-88,-14	6.08		
CE: L Cerebellum (lobule 6)	-8,-68,-10	5.48		
b L Cerebellum (lobule 6)	-32,-54,-24	5.48	327	0.05
B) FHD>HV				
a L Lingual Gyrus(BA 19, 18)(extending bilaterally)	-18,-82,-16	4.01	2092	0.031
CE: L Dentate nucleus	-16,-42,-36	3.7		
CE: L Cerebellum (lobule 6)	-12,-70,-18	3.56		
b ROI analysis: L Sensorimotor areas (BA 3,4)	-42,-36,62	3.17	25	na

BA = Brodmann area; CE = cluster extension; BL = bilateral, L = left, R = right. ROI analysis: mask over left sensorimotor area, uncorrected threshold at $p < 0.05$ with 20 voxels as extent threshold.

Table 5

Anatomical localization of clusters for the functional connectivity analysis of the left anterior putamen. Lower case letters of the first column refer to anatomical views displayed in Figure 4A, B and C.

Anatomical Regions	MNI Coordinates of local maxima (x,y,z)	T-score of local max	Volume (# voxels)	p value (FDR)
A) HV: Individuated>Coupled				
a R Superior and Middle Occipital Gyri (BA 17,18,19)	16,-92,24	6.09	1428	0.0001
CE: L Superior and Middle Occipital Gyri (BA 17,18,19), L Cuneus	-16,-94,24	5.76		
b CE: R Cuneus (BA 19)	14,-90,34	5.69		
B) FHD: Individuated>Coupled				
a R Precentral Gyrus (BA 4,6), R Postcentral Gyrus (BA 1,2,3)	36,-18,70	7.61	8585	0.0001
b CE: L Cerebellum (lobule 4,5), L and R Medial Inferior Occipital area	-16,-48,-14	6.88		
c CE: R Posterior Cingulate (BA 23,29,31), R and L Lingual Gyrus (BA 18,19)	6,-38,26	5.4		
d CE: L Thalamus	-12,-12,4	5.27		
CE: L Paracentral Lobule (BA 7)	-10,-32,80	5.11		
C) FHD>HV				
a L and R Supplementary Motor Area(BA 6) (L>R)	0,-10,60	4.65	2872	0.005
CE: L and R Cingulate Motor Area (BA 24)(L>R)	-12,-4,44	4.17		
CE: L Precentral Gyrus (BA 6)	-28,-18,74	4.13		
b L Inferior Occipital and Lingual gyri (BA 18,19)	-40,-52,-22	3.52	1891	0.037
c CE: L Cerebellum (lobule 6)	-32,-58,-28	3.85		
CE: L Fusiform Gyrus	-28,-28,-26	3.72		

BA = Brodmann area; CE = cluster extension; BL = bilateral, L = left, R = right. ROI analysis: mask over left sensorimotor area, uncorrected threshold at $p < 0.05$ with 20 voxels as extent threshold.