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Cortical Activation During Levitation and Tentacular Movements of Corticobasal Syndrome

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Abstract: Levitation and tentacular movements (LTM) are considered specific, yet rare (30%), features of Corticobasal Syndrome (CBS), and are erroneously classified as alien hand. Our study focuses on these typical involuntary movements and aims to highlight possible neural correlates.

LTM were recognizable during functional magnetic resonance imaging (fMRI) in 4 of 19 CBS patients. FMRI activity was evaluated with an activation recognition program for movements, during LTM, consisting of levitaton and finger writhing, and compared with the absence of movement (rest) and voluntary movements (VM), similar to LTM, of affected and unaffected arm-hand. FMRI acquisition blocks were balanced in order to match LTM blocks with rest and VM conditions. In 1 of the 4 patients, fMRI was acquired only during LTM and with a different equipment.

Despite variable intensity and range of involuntary movements, evidenced by videos, fMRI showed, during LTM, a significant ($P<0.05-0.001$) activation only of the contralateral primary motor cortex (M1). Voluntary movements of the affected and unaffected arm elicited the known network including frontal, supplementary, sensory-motor cortex, and cerebellum. Willed movements of the LTM-affected arm induced higher and wider activation of contralateral M1 compared with the unaffected arm.

The isolated activation of M1 suggests that LTM is a cortical disinhibition symptom, not involving a network. Higher activation of M1 during VM confirms that M1 excitability changes occur in CBS. Our study calls, finally, attention to the necessity to separate LTM from other alien hand phenomena.

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Abbreviations: AH = Alien Hand, BOLD = blood oxygen level dependent, CBD = Corticobasal Degeneration, CBS = Corticobasal Syndrome, DRS-2 = Dementia Rating Scale, EMG = electromyography, EPI = echo-planar imaging, FID = free induction decay, fMRI = functional magnetic resonance imaging, lM1 = left primary motor cortex, lSI = left primary sensory cortex, lSMA = left supplementary motor area, LTM = levitation and tentacular movements, M1 = primary motor cortex, MMSE = Mini Mental State Examination, NPI = Neuropsychiatric Inventory, PSP = Progressive Supranuclear Palsy, rM1 = right primary motor cortex, ROIs = regions of interest, RR = real rest, rSI = right primary sensory cortex, rSMA = right supplementary motor area, SMA = supplementary motor area, VM = voluntary movements, VM-l = left voluntary movements, VM-r = right voluntary movements.

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INTRODUCTION

Corticobasal Syndrome (CBS) is a term coined to indicate the presence of predominant progressive asymmetric rigidity and apraxia, which may be due to different underlying pathologies, including Corticobasal Degeneration (CBD), Alzheimer, Frontotemporal lobar, Progressive Supranuclear Palsy (PSP), and prion diseases.[1,2] CBS is mostly seen with asymmetric brain atrophy.[3,4]

Alien Hand (AH) is listed among possible symptoms of CBS,[3] in the recent revision of criteria for the diagnosis of CBS and CBD, yet "what behaviors constitute alien limb phenomena remains a matter of debate."[3]

In previous categorization reviews, AH experts[5,6] suggested that the term AH is, in the case of CBS-CBD, a "misnomer" used to describe that, in these diseases, "the arm levitates spontaneously, sometimes with tentacular movements of the fingers." These levitation and tentacular (writhing–wriggling fingers) movements are considered specific for CBS-CBD, while AH, resulting from frontal or parietal or callosal lesions, should only be identified when the specific "sensation that the limb is foreign" occurs (Real AH) or when the hand "acts at cross purposes with the will of the patient" (Anarchic Hand, or diagonistic dyspraxia,[5,6] from the greek words δια−αγΩ to carry over, separate, divert). Actual categorizations of AH describe different forms following vascular or neoplastic lesions of supplementary motor area (SMA), anterior cingulate, corpus callosum, anterior prefrontal cortex, parietal cortex, and thalamus.[5–7] AH is also identified as "alien hand sign," "main étrangère," "anarchic hand," "way-ward hand," and "diagonistic dyspraxia"[5–7] and categorizations support the division of AH in a posterior/sensory form,[8] dependent on a posterior callosal or parietal lesions; in a callosal subtype,[9] mostly characterized by intermanual conflicts (agonistic or diagonistic dyspraxia); and in an anterior/motor form, due to callosal or frontal lobe lesions (anarchic hand).[10,11] Mixed forms have also been recognized.[12]

Phenomenologically, AH symptoms consist of the subjective feeling that the hand does not belong to the patient, that is, real alien hand, because of perception of extraneousness,[6] or posterior/sensory type, which is also defined as partial somatoagnosia,[5–7] or consist of actions contrary or opposite to actions of the contralateral hand (diagonistic dyspraxia – callosal), or of propositive (goal-directed) movements that

the patient does not perceive as initiated or controlled by his own will (anarchic hand- anterior-frontal).[6]

The Pseudo-Alien hand movement of Corticobasal Syndrome is characterized by unilateral, involuntary, movements of the upper limb and hand, including levitation, considered specific by most authors,[5,6,13] and tentacular movements of hand and fingers (ie, writhing, wriggling).[13]

It is not sufficiently clear whether, beyond the specific levitation and tentacular finger movements, involuntary movements of CBS may also consist of complex manipulations, not just fondling and grasping, or of intermanual conflicts, like callosal or frontal AH. It is also not clearly described in the literature whether CBS patients experience the feeling "that the limb is foreign," as in real-posterior AH. This is not surprising though, as CBS is also characterized by cortical sensory symptoms (ie, extinction). It must be reminded that, conceptually, the presence of cortical sensory symptoms, that is, apperceptive defects,[14] should forbid to use the term "real alien hand" in CBS, as real alien hand is a local somatoagnosia, and any definition of agnosia demands, as a prerequisite, that afferential perception is normal.[15] Furthermore, the definition of agnosia requires also that cognition is unimpaired, whereas CBS is mostly described in neurodegenerative diseases which implicate cognitive decline. A recent detailed review of AH due to different aetiologies[16] evidenced that cortical sensory symptoms were present in only 40% of CBS patients with AH, and that intermanual conflicts were evidenced in less than 7% of them.

Two single case reports,[4,17] moreover, attributed to AH the occurrence of peculiar triggered (reflex) movements in CBS-CBD patients: yet, these triggered (stimulus-bound) movements are not described in consensus studies on CBS and are not currently accounted as Alien Hand phenomena.

Our study is focused exclusively on the involuntary Levitation and Tentacular Movements of CBS (LTM), in the attempt to separate these specific involuntary movements from any other AH phenomena, which may, or may not, occur in CBS.[3,5,6,13]

LTM occur only in 30% of CBS patients and only for a few months to a few years, disappearing with disease progression "when severe dystonia and rigidity supersede,"[1] in contrast with AH which may persist indefinitely.[6] In CBS the different levitation and tentacular finger movements appear intermixed with variable patterns, durations, frequencies, in unpredictable clusters lasting for seconds–minutes. The involvement of different muscles appears also variable, including hand, but also arm and shoulder muscles.[6,18]

Our purpose is to highlight possible neural correlates of LTM, as the functional mechanism underlying its occurrence is unknown. Inferential conclusions obtained from studies not including imaging evaluations during LTM suggested that, in CBS, disinhibition of cortical areas or basal ganglia circuits,[19–21] or increased functional connectivity[22] between different cortical areas might underlie the involuntary movement.

MATERIAL AND METHODS

The study was approved by Local Institutional Ethics Committee and was carried out according to the Declaration of Helsinki and its later amendments. The patients signed a written informed consent to participation to videos.

PATIENTS

During the years 1998 to 2015, 19 patients observed in our Movement Disorder clinic, serving a 3 million inhabitants catchment area, were classified as affected by CBS and probable CBD: in all MRI showed patterns of asymmetric fronto-parietal brain atrophy,[3] no signs of other neurodegenerative or vascular disorders. In all, asymmetric rigidity and apraxia were observed and none had eye movement disorders but delayed saccades-antisaccades. Absent response to L-dopa was confirmed with acute and chronic challenges.[23] Six patients presented with myoclonus. LTM was present in 7 patients (37%). Alien lower limb was observed in 1 patient. Distraction and entrainment maneuvers, performed according to current didactic methodologies,[24] could not modify the frequency, amplitude, or sectorial muscle involvement of LTM (Fig. 1, supplemental video).

Three patients were not admitted to the present functional MRI (fMRI) study, 1 because LTM was inconsistently present and subsided, substituted by melokinetic apraxia/severe dystonia during preparation to the study, 1 because of presence of metallic prostheses, 1 because agitation prevented adequate fMRI acquisition. Our study therefore is not a simple case series as, in order to be admitted to the fMRI study, each patient (4 out of 19) was selected on the basis of the presence, during fMRI acquisitions, of frequent recognizable LTM, uncontaminated by other artifacts. In order to clarify the target of our study, beyond the videos, we are presenting in Figure 1 a representation of examples of LTM.

The 4 selected patients were 1 man (54 year old, case no. 1) and 3 women (56, 67, and 70 year old, case nos. 2, 3, and 4). Duration of symptoms was 14 to 22 months when the patients were studied.

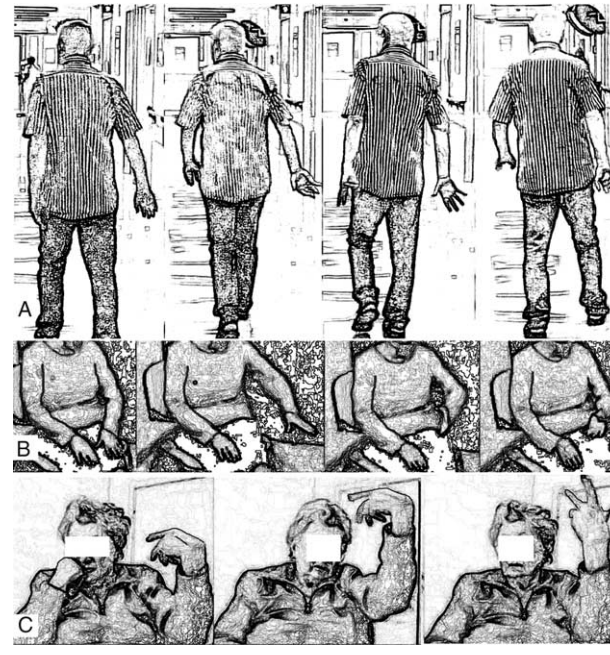

FIGURE 1. Examples of the actual analyzed levitation and tentacular movements reproduced after blurring of video images. A, Posterior levitation with finger writhing while walking, right arm. B, Lateral levitation, with elbow, hand, and finger movements, during performance of a rhythmic tapping test (entrainment manoeuvre). Compare with videos in supplementary material. C, Anterior and superior elevation of arm with finger writhing and wrist movements.

At the time of fMRI study, 2 patients (case nos. 1 and 2) had cortical sensory loss (extinction to bilateral stimuli or when the hand was concealed); 2 patients (case nos. 3 and 4) had word-finding difficulties; none of the patients had myoclonus, 2 patients (case nos. 1 and 3) showed dysexecutive symptoms, 1 (case no. 2) had memory complaints.

Each patient was followed regularly after admission to the study (for 3–6 years) in order to confirm or challenge diagnosis. Each patient was also evaluated by independent University Clinics of our country or France. At the end of follow-up the clinical diagnosis of CBS was confirmed in all patients. During follow-up LTM subsided after 2 to 3 years in all patients; cortical sensory loss and worsening of rigidity and apraxia and of cognition was found in all. All patients could be classified as affected by "probable CBS" according to recent criteria.[3]

Table 1 summarizes the characteristics of each patient and the main features of LTM. A tentative rating scale on the severity of LTM is shown in Table 2, based on the width of arm displacement observed during levitation and the frequency of tentacular (writhing) finger movements. Asymmetric brain atrophy typical of CBS[3] was prominent contralaterally to the alien limb.[4]

Clinical and Neuropsychological Examinations

Rigidity was rated with the specific item of UPDRS-III motor subscale.[25] Limb apraxia was evaluated according to reported methods for ideomotor, ideatory, melokinetic apraxia.[26] Cognition was assessed by means of Dementia Rating Scale (DRS-2)[27] and the Mini Mental State Examination (MMSE). Behavioral disorders were rated with the neuropsychiatric inventory (NPI).[28] Each of these tests was regularly repeated every 3 to 6 months during follow-up.

Neurophysiological Examinations

In all patients the pattern of LTM was monitored by surface electromyography (EMG), and recordings of EEG activities preceding the movement were attempted by means of back averaging techniques.

In none of the cases the EMG recordings evidenced regular patterns of activation that could be used to trigger fMRI acquisition nor any evidence of readiness potential could be obtained in relation with LTM, same as reported in previous studies.[29,30]

Clinical Presentation at the Time of fMRI Acquisition

Videos 1–4 show LTM at the time of fMRI acquisitions. [Video 1. LTM (case no. 1). Notice writhing movements, posterior levitation, levitation, and elbow flexion when walking. A follow-up video after 6 years can be obtained by writing to athomas@unich.it or onofrj@unich.it. Video 2. LTM (case no. 2). Notice finger writhing and fondling movements and

TABLE 1. Characteristics of Selected Patients and Main Features of LTM

	Case No. 1	Case No. 2	Case No. 3	Case No. 4
Age	54	56	67	70
Sex	M	F	F	F
Handedness	R	R	R	R
LTM side	L	L	L	R
Duration of CBS prior to fMRI (mo)	22	20	14	21
Duration of LTM prior to fMRI (mo)	9	10	12	8
LTM characteristics, movement type:				
Levitation	Y	Y	Y	Y
Finger writhing	Y	Y	Y	Y
Sensation of movement (perceived when not looking at)	N	N	Y	Y
Intermanual conflict, goal directed movements	N	N	N	N
Other CBS symptoms at the time of fMRI recording	Rigidity, Apraxia, sensory loss	Rigidity, Apraxia, sensory loss, intentional tremor, Bradykinesia	Rigidity, Apraxia, Anomia	Rigidity, Apraxia Anomia
MMSE	30	24	28	26
DRS-2	127	108	116	112
UPDRS-III	26	18	19	22
NPI	28	32	24	21
Follow-up duration (years)	5	3	3	6
CBS symptoms at end of follow-up	Rigidity, Apraxia, Sensory Loss, Aphasia, Dystonia, Bradykinesia, Myoclonus	Rigidity Apraxia, Sensory Loss, Anomia, Dystonia, Bradykinesia Tremor	Rigidity, Apraxia, Sensory Loss, Aphasia, Dystonia, Bradykinesia	Rigidity, Apraxia, Sensory Loss, Aphasia, Dystonia, Tremor, Bradykinesia

LTM indicates only levitation and tentacular movements (finger writhing). Notice that the table reports, although absent, also some of the features of real alien hand, that is, sensation and finalized gestures. CBS = Corticobasal Syndrome, DRS-2 = Dementia Rating Scale-2, fMRI = functional magnetic resonance imaging, LTM = levitation and tentacular movements, MMSE = Mini Mental State Examination, N = absent, NPI = neuropsychiatric inventory, UPDRS = Unified Parkinson Disease Rating Scale, Y = present.

TABLE 2. LTM Rating Scores: Tentative Categorization. Tentative Rating Scale on the Severity of Levitation and Tentacular Movements and Possible Alien (Anarchic) Hand Phenomena in Corticobasal Syndrome

	Case No. 1	Case No. 2	Case No. 3	Case No. 4
Movement type				
Levitation	Y A1	Y A1	Y B3	Y A1
Tentacular movements	Y F2 W1	Y F2 W2	Y F3 W3	Y F1 W1
Fondling (bed sheets, clothes)	Y1	Y1	Y1	Y1
Grasping (palm stimuli)	N	N	N	N
Goal directed movements	N 0	N 0	N 0	N 0
Inter-manual conflict	N 0	N 0	N 0	N 0

Levitation: posterior or lateral displacement, involving limb abductors: A-tonic B-phasic—1, below mid thorax; 2, above mid thorax; 3, above shoulders. Tentacular Finger (F) movements: 1, sporadic in a 5-min evaluation; 2, recurring in less than 2-min evaluation; 3, recurring-subcontinuous with less than 60-s relapses. Wrist (W) movements: 1, sporadic; 2, constantly accompanying finger movements. Fondling (grasping of bed sheets or clothes during examination): 1, sporadic in 30-min evaluation; 2, more than 5 times in 30 min. Grasping (palmar stimuli with examinators hands or objects). Goal-directed movements: 0, absent in 30-min evaluation; 1, present. Diagonistic dyspraxia-intermanual conflict: 0, absent in 30-min evaluation during tasks of the Unified Dyskinesia Rating Scale; 1, present. LTM = levitation and tentacular movements, N = absent, Y = present.

levitation of the left arm, unaffected by tapping movements of the right arm. The video documents, also, a short part of apraxia assessment, when the patient was asked to show the movement performed when using a screwdriver. Video 3. LTM (case no. 3). Complex continuous LTM. Initially the patient holds her hand, then free movements are allowed. Notice that she holds with the right hand her left arm with LTM, this cannot be considered diagonistic dyspraxia (intermanual conflict), which should indeed be identified if the holding movement was of the left hand. Notice finger writhing, wrist flexion, levitation with elbow flexion, the hand is often moved above the head. Video 4. LTM (case no. 4). Patient videoed in 1998. Notice abduction and levitation when walking. Writhing and levitation during apraxia examination, superimposed dystonia, and attempts to hold the hand. A follow-up video after 1 year showing dystonia, posterior levitation, and a video performed during fMRI (different equipment and method than the first 3 patients) can be obtained by writing to athomas@unich.it or onofrj@unich.it.]. Figure 1 shows examples of the movements.

Patients 1, 2, 3 presented with left arm LTM (supplemental videos 1, 2, 3, http://links.lww.com/MD/A498, http://links.lww.com/MD/A499, http://links.lww.com/MD/A500), patient 4 presented with right arm LTM (supplemental video 4, http://links.lww.com/MD/A501). All LTM consisted of finger writhing and levitation appearing, variably intermixed, in clusters lasting for 10/120 s, followed by 5/600 s of absence of LTM. During the clusters the approximate frequency of writhing (tentacular finger movements) was 0.5 to 1 Hz, levitation was a constant ''tonic'' pattern lasting throughout the whole cluster in patients 1, 2, and 4. In patient 3 levitation involved also shoulder muscles and induced raising of the arm above the head, concomitant with finger writhing and wrist rotation (supplemental video 3, http://links.lww.com/MD/A500) with an approximate frequency of 0.3 to 0.5 Hz. In all patients also grasping and fondling was observed sporadically, mostly when the hand was in contact with clothes. Grasping was not analyzed in the present fMRI study, as any tactile stimulus was avoided during fMRI acquisition.

FMRI Acquisition

Functional and anatomical images of case nos. 1, 2, 3 were acquired with a Philips scanner at 1.5 T by means of T2*-weighted echo planar imaging with repetition time of 2.5 s, voxel size 4×4×4 mm and T1-weighted 3D respectively.

During fMRI acquisition patient arms and forearms were blocked along their body side by means of strips in a plastic tray allowing elevation by 10° of the forearm and movements of the hand. The patients could not see their hands during the experiments. The patient was asked to rest, to move left arm, to rest, to move right arm, alternating rest and voluntary movement (VM) every 30 s. During the voluntary movement of the arm the patient had to lift the hand to the limit allowed by the strip, and perform for 30 s flexion–extension of the fingers (wriggling) with an approximate frequency of 1 movement every 2 s. Each fMRI session consisted of 2 runs. In each run 180 volumes (2.5 s per volume) are acquired alternating 12 volumes of rest (30 s) and 12 volumes of VM for 5 times, for a total of 60 volumes of rest, 60 volumes of right hand movements, and 60 volumes of left hand movements.

During fMRI acquisitions 3 different movement disorders experts observed the left hand for presence of movements akin to LTM movements observed prior to recording session. Only movements that were evaluated as LTM by all the 3 examiners (100% concordance) were considered for analysis. The examiners marked volumes acquired during rest without any movement, and during rest periods in which LTM occurred, and volumes corresponding to VM during which also LTM or any other movement not matching the task had occurred.

Case no. 4 was recorded in 1998 with a Siemens Magnetom equipment. FMRI sequences were of the echo-planar imaging (EPI) free induction decay (FID) type with TR 5 s, TE 54 ms, flip angle 90°. Functional imaging volumes were acquired continuously during rest conditions in blocks lasting 30 s each for 15 min. Simultaneous visual inspection identified LTM and marked acquisition blocks where LTM occurred and rest blocks without LTM. Post-hoc analysis could compare 5 blocks (150 s) of acquisition corresponding to LTM and 5 blocks of rest conditions without LTM. Blocks contaminated by other artefacts, linked to any bodily movement performed by the patient during acquisition, were discarded.

We did not ask to perform any VM task at that time, because data were collected as, preliminary, observational evaluations, because LTM superseded, substituted by dystonic posture, and because we were surprised by the findings (as we were expecting to observe basal ganglia activation), and we decided to wait for new cases, challenging or confirming the first finding.

FMRI Analyses for Case Nos.1, 2, 3

FMRI data analyses were carried out using Brain Voyager Qx software. Preprocessing of functional scans included 3-dimensional motion correction and removal of linear trends from voxel time series. Functional volumes of each patient were coregistered with the corresponding structural data. Structural and functional volumes were transformed into the Talairach space using a piecewise affine and continuous transformation. For the statistical analysis volumes in which VM was contaminated by LTM or other movements artefacts were discarded, and the amount of volumes acquired during LTM were balanced with volumes acquired during rest and VM. The final comparison consisted of 3 blocks of 12 volumes (90 s) of LTM, 3 blocks of 12 volumes (90 s) of rest without any movement (Real Rest-RR), 3 blocks of 12 volumes (90 s) of left VM (VM-l), and 3 blocks of 12 volumes (90 s) of right VM (VM-r) for the case no. 1; 4 blocks of 12 volumes (120 s) for each condition for case no. 2; 5 blocks (150 s) for each condition for case no. 3.

FMRI Analyses for Case No. 4

Analysis was performed using MEDx software package (Sensor Systems, Sterling, VA). After correction of motion artifacts, statistical brain activation images were generated by a Student paired *t* test comparing, voxel by voxel, images of the LTM condition to those of the rest condition. A cluster detection algorithm implemented in MEDx was run to select significantly activated ($P<0.05$) clusters of voxels. Activation map was superimposed on the high-resolution structural image transformed into Talairach space with the MEDx procedure. MEDx software and the same methodological approach as applied in the present study were used to compare block paradigm fMRI acquisitions in previous papers.[31,32]

Statistical Analysis

Statistical analysis was performed for each patient separately using the general linear model on all cortical and subcortical areas including frontal and parietal cortex, SMA, basal ganglia, and cerebellum.[33] The comparison was between LTM vs. RR, VM-l vs. RR, VM-r vs. RR, and VM-r vs. VM-l. The evaluation of VM was performed using a well-known standard presurgical procedure.[34–39]

To account for the hemodynamic delay, the boxcar waveform representing the rest and task conditions was convolved with an empirically founded hemodynamic response function.[40,41]

As the comparison was intrasubject, no comparisons were made to healthy controls.

Analyses included standard group analysis[34] among case nos. 1, 2, 3 and regions of interest (ROIs) analysis. Group analysis was performed for the VM-l vs. RR, LTM vs. RR, and VM-r vs. RR.

ROI analysis is most often applied for the analysis of activations, but it can be equally useful to determine the reasons for lack of activation.[42] In the present study clusters of activation identified from group analysis of case nos. 1, 2, 3 during VM-l condition compared with RR were used as ROIs to measure the percentage of the blood oxygen level dependent (BOLD) signal during voluntary and LTM.

We also used single-subject (*t* statistic) analysis on fMRI data to study intersubject variability of activated areas, to study the correspondence between anatomy and activation, and to guarantee that activated areas during LTM were identifiable in individual subjects.[34] Single-subject analysis guarantees that specific activations of brain areas are present in all the studied subjects; thus the results are not simply inferred from group analysis.[34,43]

Each statistical map had a threshold at $P<0.05$ (analyses were also performed for each map at thresholds of $P<0.1$ and $P<0.01$) to test specificity and sensitivity of the findings, higher than thresholds used in presurgical procedures to evaluate activation of M1 during voluntary movement,[34–39] was Bonferroni corrected and superimposed on the anatomical scans for the localization of significantly activated areas in the contrast between VM-l vs. RR, VM-r vs. RR, and LTM vs. RR. Accurate corrections for multiple tests were performed to avoid significance by chance, due to the large number of voxels from whole-brain analysis.[44]

RESULTS

Case Nos. 1, 2, 3

Voluntary Movements

During the VM-r vs. RR all patients showed clusters of activation located in the left primary motor cortex (lM1), left premotor cortex, left primary sensory cortex (lSI), left SMA (lSMA), and right cerebellum, according to the Talairach atlas ($P<0.01$). For all patients the intensity (peak change of the BOLD signal) and the spatial extent (number of activated voxels) of the clusters were higher in the motor area than in the other activated regions.

During the VM-l versus RR all patients showed clusters of activation located in the right primary motor cortex (rM1), right premotor cortex, right primary sensory cortex (rSI), right SMA (rSMA), and left cerebellum, according to the Talairach atlas ($P<0.01$).

VM-r and VM-l elicited also other cortical areas for all patients. Table 3 shows the Talairach coordinate of the center of the clusters, the peak *t* value of activation, the maximal BOLD signal change in percentage of all activated clusters, the number of voxels for each cluster.

Figure 2 shows the activation maps ($P<0.01$, corrected) in the contrast of VM-r vs. RR and of VM-l vs. RR for all cases.

The statistical contrast between VM-l and VM-r showed higher intensity (peak *t* value and BOLD signal change), and larger extension of the activity (number of activated voxels) in the rM1 than in the lM1 for all patients. At the same threshold value, the percentage increase in the number of activated voxel of the rM1 than of the lM1 was approximately 53%, 20%, and 63% for the case nos. 1, 2, and 3 respectively. Figure 3 shows a larger involvement of the rM1 during the voluntary movement of the affected (left) hand than the lM1 during the voluntary movement of the unaffected (right) hand for a representative patient (case no. 2).

No differences were found on intensity and extension of clusters in contralateral premotor, contralateral SI, contralateral SMA, and ipsilateral cerebellum between VM-l and VM-r.

Both group and single subject analysis showed the activation of a network which included frontal, parietal, temporal areas, and cerebellum. The peak of the percentage of the BOLD signal across patients ranged from 0.2 to 1.7 across ROIs. The largest magnitude among areas was found for the contralateral motor cortex. Similar values of BOLD signal were found in other fMRI studies.[45]

LTM

The statistical contrast between LTM and RR showed in each patient the selective activation of the rM1 ($P<0.01$). No

TABLE 3. fMRI Results. Talairach Coordinate of the Center of the Clusters, the Intensity of the Peak of Activation, the Maximal BOLD Signal Change in Percentage of All Activated Clusters, the Number of Voxels for Each Cluster for the Voluntary and Involuntary Movements Vs Real Rest

	Contrast	Brain Region	*x*, *y*, *z* (mm)	Peak *t* Value	Peak Change BOLD Signal (%)	No. of Voxels
		Frontal				
		Rpremotor	33, −15, 53	10.7	1.22	404
		RM1	44, −22, 53	22.3	1.91	975
		RSMA	9, −19, 48	12.6	0.96	391
		Rinferior frontal	47, 21, 24	12.1	0.72	51
		Lmiddle frontal	−40, 25, 26	9.3	0.91	30
	VM-l > RR	Parietal				
		RSI	35, −41, 41	12.1	0.64	465
		RSII	53, −36, 28	14.9	1.22	289
		LSII	−61, −23, 14	14.4	1.27	308
		Rinferior parietal lobe	41, −52, 41	13	0.79	548
		Other cortical and subcortical				
		Rtemporal	57, −46, −10	13.7	0.99	636
		Lcerebellum	−15, −53, −17	13.8	1.14	716
Case no. 1	**LTM > RR**	**RM1**	**43, −20, 52**	**7.5**	**0.81**	**78**
	VM-r > RR	Frontal				
		Lpremotor	−39, −15, 53	20.1	1.51	386
		LM1	−42, −21, 50	20.6	1.26	635
		LSMA	−10, −15, 48	15.1	0.79	362
		Lmiddle frontal	−22, 42, 25	9.9	0.93	67
		Rmiddle frontal	36, 32, 28	9.8	0.53	39
		Parietal				
		LSI	−40, −43, 51	14.4	1.13	433
		LSII	−55, −39, 19	14.6	1.18	556
		Linferior parietal lobe	−50, −46, 28	15.8	0.81	374
		Other cortical and subcortical				
		Rtemporal	57, −45, −8	13.7	1.23	874
		Rcerebellum	17, −52, −17	16.2	1.58	681
		Frontal				
		Rpremotor	37, −11, 55	17.3	0.70	260
		RM1	34, −25, 57	24.3	1.36	917
		RSMA	3, −17, 55	19	1.19	842
		Rmiddle frontal	41, 33, 29	12.9	0.71	47
		Lmiddle frontal	−42, 26, 30	8.6	0.88	18
	VM-l > RR	Parietal				
		RSI	41, −38, 47	15.6	0.45	741
		RSII	44, −29, 12	10.4	0.75	141
		Other cortical and subcortical				
		Rtemporal	53, −54, 5	10	0.44	94
		Lcerebellum	−13, −51, −14	22.5	1.00	588
Case no. 2	**LTM > RR**	**RM1**	36, −26, 58	9.2	0.65	159
		Frontal				
		Lpremotor	−29, −10, 54	10.3	0.87	183
		LM1	−35, −28, 57	25	1.51	765
		LSMA	−2, −17, 56	21.3	1.00	614
		Lmiddle frontal	−30, 35, 29	8.8	0.44	31
		Rmiddle frontal	43, 31,25	11.7	0.55	23
	VM-r > RR	Parietal				
		LSI	−39, −46, 48	15.2	0.38	492
		LSII	−49, −40, 16	12.8	0.39	64
		Other cortical and subcortical				
		Ltemporal	−46, −59, 6	14.4	0.49	17

	Contrast	Brain Region	*x*, *y*, *z* (mm)	Peak *t* Value	Peak Change BOLD Signal (%)	No. of Voxels
		Rcerebellum	4, −57, −11	21	0.85	465
		Frontal				
		Rpremotor	26, −20, 51	6	0.82	132
		RM1	35, −25, 55	13.8	1.66	494
		RSMA	2, −5, 42	9.4	0.95	118
	VM-l > RR	Parietal				
		RSI	31, −44, 37	10.8	0.68	416
		Other cortical and subcortical				
		Lcerebellum	−14, −51, −24	20.6	0.80	799
	LTM > RR	**RM1**	**35, −23, 54**	**8.1**	**0.48**	**124**
Case no. 3		Frontal				
	Lpremotor		−28, −15, 57	6.5	0.23	51
	VM-r > RR	LM1	−31, −26, 54	7	0.75	302
		LSMA	−9, −12, 52	3.9	0.60	75
		Linferior frontal	−24, 38, 10	8.4	0.36	134
		Parietal				
		LSI	−41, −35, 50	8.3	0.39	152
		Other subcortical				
		Rcerebellum	20, −51, −25	9.3	1.23	410
Case no. 4	**LTM > RR**	**LM1**	**−34, −26, 52**	**5.4**	**0.52**	**88**

BOLD = blood oxygen level dependent, fMRI = functional magnetic resonance imaging, LM1 = left primary motor cortex, LSI = left primary sensory cortex, LSII = left secondary sensory cortex, LSMA = left supplementary motor area, LTM = levitation and tentacular movements, M1 = primary motor cortex, RM1 = right primary motor cortex, RR = Real Rest, RSI = right primary sensory cortex, RSII = right secondary sensory cortex, RSMA = right supplementary motor area, SMA = supplementary motor area, VM-l = left voluntary movements, VM-r = right voluntary movements.

evidence of activation was found in other cortical or subcortical areas. Even at higher *P* value (lower threshold) ($P<0.05$, $P<0.1$), no significant activation was found in any other cortical area in any patient. In addition, when lower threshold ($P<0.1$) was applied, isolated voxels of activations were found located outside the brain and the skull, indicating that the results were unreliable at very low threshold (Supplemental Figure 1, http://links.lww.com/MD/A502).

The isolated activation of the contralateral M1 during LTM is shown in Figure 2.

Group analysis on LTM vs. RR showed the isolated activation of the rM1. ROIs analysis during LTM showed a clear increase of the BOLD response only for the rM1. No evidence of changes was found in frontal, SMA, parietal cortex, and cerebellum, suggesting that the lack of activation in other brain areas during LTM was not related to whole-brain

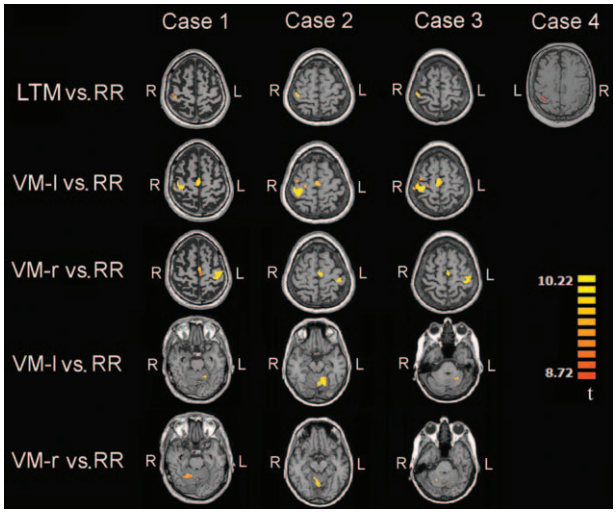

FIGURE 2. fMRI results for the different conditions. Activation maps for LTM vs. RR in all cases. Activation maps for VM-r vs. RR and for the VM-l vs. RR for case nos. 1, 2, and 3.

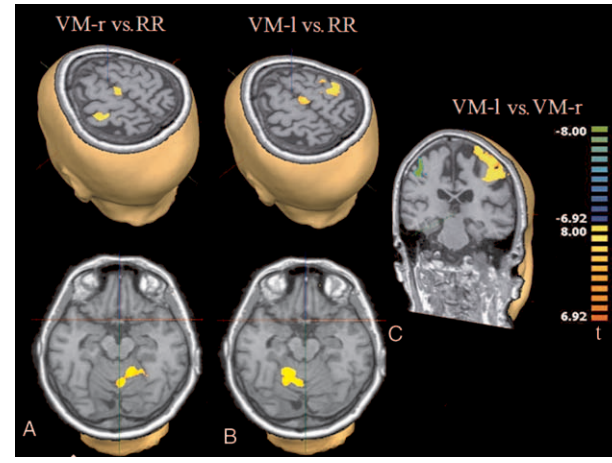

FIGURE 3. fMRI results from case no. 2. Three-dimensional activation maps for VM-r vs. RR (A) and for VM-l vs. RR (B). Comparison of M1 activation (C) during voluntary movements (green, right-hand movement, yellow left-hand movement). Notice the wider extension of the cluster of activation in the rM1 than in lM1.

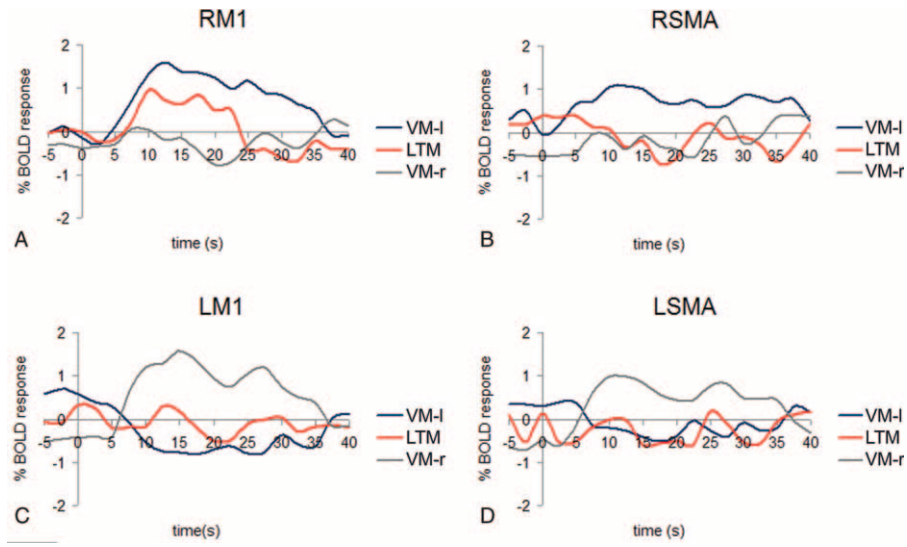

FIGURE 4. Timecourses of the BOLD signal in percentage for the right primary motor cortex (rM1, A), right supplementary motor area (rSMA, B), left primary motor cortex (lM1, C), and left supplementary motor area (lSMA, D) during the voluntary movement of the left hand (VM-l), the LTM of the left hand, and the voluntary movement of the right hand (VM-r). Notice that no significant increase of the BOLD response was found in SMA during LTM.

voxel-wise comparison between movement and rest or thresholded activation maps.

Figure 4 shows the time courses of the percentage of the BOLD signal for each condition (VM-l, VM-r, LTM) for the following selected ROIs: lM1, rM1, lSMA, and rSMA.

LTM and VM Comparisons

For all patients, the location of the peak activity within rM1 was similar during LTM and voluntary movement of the left hand; indeed no significant difference was found in the comparison across coordinates. Significant difference was instead found in the comparison between the intensity and extension of activation within contralateral M1 during left and right voluntary and left LTM. The BOLD signal change and the number of activated voxels were lower during LTM than VM of the left and right hands (Table 3).

Case No.4

The statistical contrast ($P<0.05$) between LTM of the right hand and RR showed the selective activation of the lM1. Figure 2 shows the activation of lM1 during the LTM vs. RR. Table 3 shows the Talairach coordinate of the center of the cluster, the intensity of the peak of activation, the maximal BOLD signal change in percentage, and the number of activated voxels for the lM1.

SYNTHESIS

LTM were accompanied only by activation of contralateral M1.

Group analysis could be performed only in the three patients whose data were acquired with Philips magnetom. The fourth patient was studied in 1998 with a different equipment; nonetheless, fMRI during LTM showed activation of the only contralateral M1 area. Different thresholded activation maps, single-subject analysis, ROIs analysis, all showed absence of any other activation. During voluntary movements, analyzed in the 3 patients, fMRI evidenced activation of the known motor network[34–39] including M1, S1, SMA, prefrontal cortex, and cerebellum. Yet, the comparison between voluntary movements of the affected and unaffected sides showed that M1 activity was statistically higher for the affected side.

DISCUSSION

Our exploratory fMRI acquisition shows results obtained during the involuntary movements in 4 CBS patients presenting with consistently recognizable (as shown by videos) LTM.

Our study shows that LTM correlates with isolated activation of contralateral M1 (Fig. 2, Table 3): all 4 patients showed the same pattern of isolated activation, despite involuntary movements appearing with different intensity, frequency, range of arm displacement (supplemental videos 1–4, http://links.lww.com/MD/A498, http://links.lww.com/MD/A499, http://links.lww.com/MD/A500, http://links.lww.com/MD/A501) and despite different fMRI equipment being used. Voluntary movements elicited activity in the known network consisting of multiple cortical areas and cerebellum.[34–39]

Several statistical approaches (ie, lowering thresholds, single-subject and group analyses, ROIs analysis) evidenced that the effect was not dependent on low power or threshold of activation maps. The activation of the network during willed (task provoked) movements, which were of smaller range amplitude than involuntary LTMs (Table 2, supplemental videos), argues against any interpretation linking the finding to sample size and comparison thresholds. As evident from Table 3, a threshold of area detection for BOLD signal changes in other areas than M1 was as low as 0.23%.

With this threshold the BOLD signal changes in M1 during LTM were by 71 to 52% lower than activation of M1 during voluntary movement. BOLD signal changes in areas different than M1 during voluntary movement were lower by 68 to 22% than activation in M1 during voluntary movement. We suggest that it is unlikely that with such a high power of signal detection any activated areas could have been invariably concealed in all the patients.

In our CBS patients, intensity and extent of M1 activity was increased during the voluntary movement of the LTM affected hand, in comparison with voluntary movement of the unaffected hand (Figure 3C). This finding could be interpreted as dependent on hyperactivity-disinhibition of M1 and is in agreement with previous studies, performed with other neurophysiological techniques, but unsupported by imaging studies.[19,30,46] Valls-Solé et al[19] showed in AH patients a larger extension of the cortical map of hand muscles to stimulation of the hemisphere contralateral to the AH in comparison with the ipsilateral hemisphere. These results were interpreted by the authors as enhanced excitability, or reduced inhibition, of the motor area of the hemisphere contralateral to the AH.

The specific findings of our study suggest hypotheses on the mechanism of LTM in CBS.

We suggest that LTM are due to random loss of inhibition dependent on the pathological process (frontotemporal dementia, PSP, CBD) affecting the hemisphere.[1,2] Released from the control of inhibitory inputs, M1 may produce rhythmic (pseudorhythmic) excitatory ripples, which result in LTM.

Alternative hypotheses suggested that disinhibition is due to unstable imbalance between the 2 hemispheres,[4] as dependent on the asymmetric atrophy observed in the majority of cases with CBS; however, the atrophy, in some CBS cases, is bilateral, and involuntary movements can also be bilateral.[4,6]

The finding of isolated M1 activity during LTM appeared to us as unexpected. In fact, CBS involuntary movements, disappearing in a few months and replaced by dystonia and rigidity, were considered as originating in the basal ganglia,[20,21,47] according to the model proposed by Marsden to explain the genesis of involuntary movements, which are supposedly due to release of movement patterns encoded in the striato-thalamic circuit.[21]

However, the original studies on functions of Area 4 (M1 cortex), and corticospinal tract, evidenced that these areas provide capacity for independent finger movements,[48] thus finger writhing may just indicate that M1 is released from the control of adjacent cortical areas. Levitation was clearly described by Denny-Brown et al,[49] in parietal lobe lesions inducing deafferentation of M1; thus also levitation might be the expression of deafferentation of M1 from parietal cortex. The same author suggested that rigidity is the mild form or precursor of dystonia, interpreted, at the time, as a peculiar form of hemiplegic spasticity.[50] On the basis of these historical studies, we may complete our hypothesis by suggesting that, in the progression of asymmetric rigidity, which is the specific core symptom of CBS, LTM appear for a restricted time period, during which deafferentation and isolation of M1 (Area 4) are prevalent among the other effects of the degenerative process. Later on, further degeneration could involve more severely M1 and other motor areas, and increase the evidence of dystonia.

A theoretical objection to our findings could argue that the movement, albeit involuntary, should elicit a sensation that should activate somatosensory perception areas: this activation was not found. We suggest that this is not unlikely, as our patients either had cortical extinction at the time of recordings, or presented it shortly after during follow-up. As reported in the Introduction, cortical sensory suppression is a core symptom of CBS, and its presence impinges on the possibility of identifying somatoagnosia, that is, Real AH. The negative finding is also not unlikely as, according to quoted Denny-Brown et al,[50] deafferentation of M1 from parietal cortex is the underlying cause of levitation.

Therefore, our findings are in agreement with concepts expressed by physiological studies on M1,[48,50] and show the unprecedented evidence of an isolated cortical activation during an involuntary, nonepileptic, movement. A prior single case report,[29] in a patient with a brain infarct, also showed isolated M1 activation during tentacular finger movements, which were inappropriately labeled as AH.

Surprisingly, the existing literature mostly does not report fMRI analysis of involuntary movements, during the actual movement, by applying protocols for movement analysis. All prior studies were performed in resting state conditions, analyzing connectivities between different areas during rest, that is, in the absence of movement, this for Chorea, Dyskinesias, and CBS.[22,51–53] All studies evidenced hyperconnectivity in the different disorders and provided theoretical explanations for the findings. This method could provide some hypothesis-driven evidences of disease-related network alterations, but cannot evidence the network activation during actual movements.

The present study, instead, applies a movement analysis protocol to an involuntary movement, and is therefore the first study to provide this information, apart from the study by Assal on a single case.[29] Actually, our first observation was acquired 7 years before the study by Assal[29] appeared in the literature, but we waited for a long time in order to collect more reproducible cases, which could confirm or confute the first findings. A recent study was performed on 36 patients affected by Tourette syndrome,[54] with the same fMRI protocol for activation detection during movements, as used in our study. The authors defined a temporal pattern of activation of several cortical areas before and in concomitance with tic production, involving sequentially the supplementary motor area (SMA), sensorimotor cortex, and several other cortical and subcortical areas. However the results were not controlled in comparison with voluntary movements nor for tic suppression[54] and it must be reminded that Tourette patients were able to suppress voluntary their tics, while LTM could not be controlled.

By showing isolated activation during involuntary LTM, we do not challenge findings obtained in resting state protocols, as the 2 conditions are, evidently, different. Yet evidence of an isolated cortical activation during an involuntary activity appears, to us, of interest, as the finding actually confirms the theory suggesting that consciousness-awareness of any action requires the activation of a complex network, not just of single cortical areas.[55,56]

We believe that activation of network is extremely unlikely during real involuntary movements as the activation of a network should represent the occurrence of some awareness[56] and thus defy confidence on involuntariness. Prior theories suggested that real involuntary movements, that is, not distractible, arise from subcortical structures.[21] Our study, supported only by the single case report by Assal et al,[29] shows that an involuntary movement can be accompanied by isolated M1 activation.

Our hypothesis is only focused on LTM, and links this movement more to rigidity than to AH. During grasping or fondling movements of AH,[13,18,19,22] sensory and premotor areas should be obviously activated. Other AH phenomena, such as intermanual conflicts and unconscious yet finalized actions, may imply the involvement of further cortical areas.

At difference with our findings, a single case study in a patient with putative CBD showed activation of multiple areas,[17] but the movement was triggered, rather than spontaneous, thus at odds with current descriptions[1,3,5,6,13,18,57] of AH and LTM. A triggered movement in CBD was also shown in

another single case report[4] (not including fMRI acquisitions): we do agree that a triggered movement will require the activation of multiple areas as, obviously, afferent and efferent areas must be activated. We do not agree however with the concept that a triggered movement may represent an example of Alien Hand or of undebatable involuntary movement. We suggest that these triggered movements represent classic and simple examples of Environmental Dependency Syndrome, or Stimulus bound behaviors,[58] which are expected in CBS as the underlying pathology, independently of the type, involves frontal lobes.[1,2] In the case of triggered movements, furthermore, the involuntary nature of movements appears peculiarly controversial, as several other elements accompanying the movements should be analyzed, and accounted for, according to theories on disorders of willed action,[59] for example, agency, intention to movement, volition. Of note, distractors or entrainment maneuvers were not tested in the 2 described, triggered, cases, while LTM were specifically not suppressed by distractors or entrainment in our patients.

Our study invites to reconsider the set of movements appearing in CBS, by separating LTM and other involuntary or triggered movements: in other words, we suggest that CBS AH could be properly studied by dissecting different sets of movements according to phenomenological categories, and by using different imaging methods according to different phenomenologies. Our study also invites to reconsider the relevance of LTM for CBS diagnosis.

In our case series of 19 patients we only observed LTM in 7, we observed fondling and grasping in all 7, but we did not observe Real AH or Frontal AH. As reported in case 3, video caption and video, we observed that the unaffected hand held the affected hand in order to restrict involuntary movements, but we did not term this movement ''intermanual conflict'' as this term should be appropriate only if the affected hand was restraining the unaffected hand.

LTM are described in several CBS-CBD case series[1,2,4,13,18,30,46,60–64] and are indicated as specific of CBS,[5,6] yet the recent revision criteria[3] overlook these phenomena, which are dismissively considered only in AH definition, ''more than simple levitation.''

We suggest that LTM should find a proper place in CBS diagnosis, and should be considered apart, as a separate entity dependent on isolated M1 disinhibition.

As already underlined by the previous literature,[6] LTM can be erroneously considered as akin to AH, or even can be erroneously labeled as AH.[6,13,29]

The introduction in CBS definition of descriptive features (as tentatively suggested in Table 2), or of specific terms like LTM, or Pseudo-AH, could help to disentangle the ''matter of debate'' regarding AH[3] in CBS. Our paper invites to apply simple descriptive phenomenological methodologies, including entrainment manoeuvres, to clarify the nature of the involuntary movements observed in CBS.

Strengths and Limitations of the Study

The selection of a specific type of involuntary movement, that is, LTM can be considered strength of the study, since it allowed to avoid the controversies around alien hand and its debatable features.

Strengths are also in the methods used for analysis, including different threshold levels and ROI analysis, and in the selection and documentation of patients among a case series of 19 patients (the study required more than 10 years to be completed). Previous controversial reports consisted of single case studies picturing different movements, described but not documented by videos. Case series were also presented[1,2,4,13,18,30,46,60–64] where only a minority of patients had actually involuntary movements and acquisitions were performed in the absence of any movement.

Limitations. Evidence of M1 isolated activity could be attributed to a putative prominence of M1 activity during any (voluntary, involuntary) movement: however M1 is not always the area of major activation during movements[65] and our comparison of LTM with voluntary movements showed activations of the entire motor network. The intensity of activation of the different areas of the motor network is related to different kinematic variables: amplitude and speed of movement,[66] discrete or continuous movements,[67] self or triggered movements.[68] In the recent Tourette study, the area with highest activity was not M1.[54] Furthermore, different threshold and ROI analysis according to correct methodologies were carefully studied in order to try to evict any possible area of activation during LTM.

Limitation could be also identified in the method for movement recognition during LTM: same as for the other studies analyzing the voluntary or involuntary movements,[29,34,54] our method consisted of visual identification of the movement by our experts. Our method was, however, reinforced by the involvement of 3 experts in LTM recognition, and by the cutoff given by 100% concordance. Our study fosters the development of acquisition method including simultaneous video recording of movements and post-hoc analysis. This methodology is not yet available.

An alternative approach may consider that our choice of selecting one specific set of movements, LTM, rather than the generic AH attributed to CBS is a limitation rather than a strength. In support of our selection we quoted the existing controversial literature and in the discussion we underlined the physiological background that supports and strengthens our findings. It is likely, obvious perhaps, that more complex AH movements would require the involvement of several areas. We augur that further studies will show and document appropriately these movements.

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