Moving with or without Will: Functional Neural Correlates of Alien Hand Syndrome

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Alien hand syndrome is a rare neurological disorder in which movements are performed without conscious will. By using functional magnetic resonance imaging in a patient with alien hand syndrome after right parietal lesion, we could identify brain regions activated during involuntary or voluntary actions with the affected left hand. Alien hand movements involved a selective activation of contralateral primary motor cortex (M1), presumably released from conscious control by intentional planning systems. By contrast, voluntary movements activated a distributed network implicating not only the contralateral right M1 and premotor cortex but also the left inferior frontal gyrus, suggesting an important role of the dominant hemisphere in organizing willed actions.

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The cerebral underpinnings of our experience of conscious will during motor actions are still poorly known and constitute one of the most challenging issues in neuroscience. Neural processes involved in the control of motor acts performed with or without intention have mainly been studied in a theoretical perspective based on models of normal motor learning and control.[1] In clinical neurology, striking deficits in the conscious control of action may arise in some patients with focal brain lesions, and such disorders provide unique opportunities to unveil the critical neural components underlying voluntary behavior. The alien hand syndrome (AHS) refers to a rare and distressing condition where a patient's hand may act without being guided by the patient's own will.[2] Patients with AHS may reach for objects and start manipulating them without wanting to do so, sometimes to the point that they present with conflicting actions (diagnostic apraxia) or must use their healthy hand to restrain the alien hand's actions.[3,4]

Several lesion sites have been reported in patients with AHS, including the supplementary motor area (SMA), anterior cingulate, corpus callosum, and/or posterior parietal cortex. This anatomic heterogeneity explains the various clinical manifestations of AHS, also sometimes referred to as "capricious" or "anarchic" hand.[2,5] In all these conditions, neural mechanisms of AHS have remained obscure or speculative. A few single-case studies using experimental neuropsychology methods have suggested a loss of volitional control combined with intact action production systems, or a conflict between the two for action selection.[6,7] Here, we used functional magnetic resonance imaging (fMRI) in a rare patient with AHS, to determine the functional neuroanatomic substrates implicated in alien movements, relative to voluntary movements (VMs), and thus identify neural processes capable of producing unwanted motor acts.

Case Report

Our patient was a 70-year-old right-handed man who presented with AHS after a large stroke in the right parietal lobe (Fig 1; white arrows). His contralesional/left hand showed relatively preserved motor function, with only slight weakness and clumsiness, but marked sensory loss. Neuropsychological examination showed no major cognitive deficits except for mild left visual neglect and tactile extinction on double stimulation. His alien movements were characterized by involuntary gestures or grasping made with his contralesional/left hand, which the patient sometimes failed to notice because of his neglect for left hemispace. For instance, his left hand could grasp and manipulate parts of clothes or objects, even tear them into pieces, while the patient was seating in his armchair and unaware of these involuntary movements.

Functional Imaging Paradigm

We performed two fMRI experiments using simple motor tasks that were easily performed by the patient and allowed us to compare similar left-hand movements executed either with or without conscious will. We exploited the fact that, when the patient was resting and otherwise inactive, his left hand would often start moving spontaneously for a period of several seconds, typically making repetitive flexion-extension movements of the fingers with a relatively slow alternating rhythm. In the first experiment, we acquired 3 fMRI sessions (6 minutes each) while the patient was required either to remain still for a variable duration

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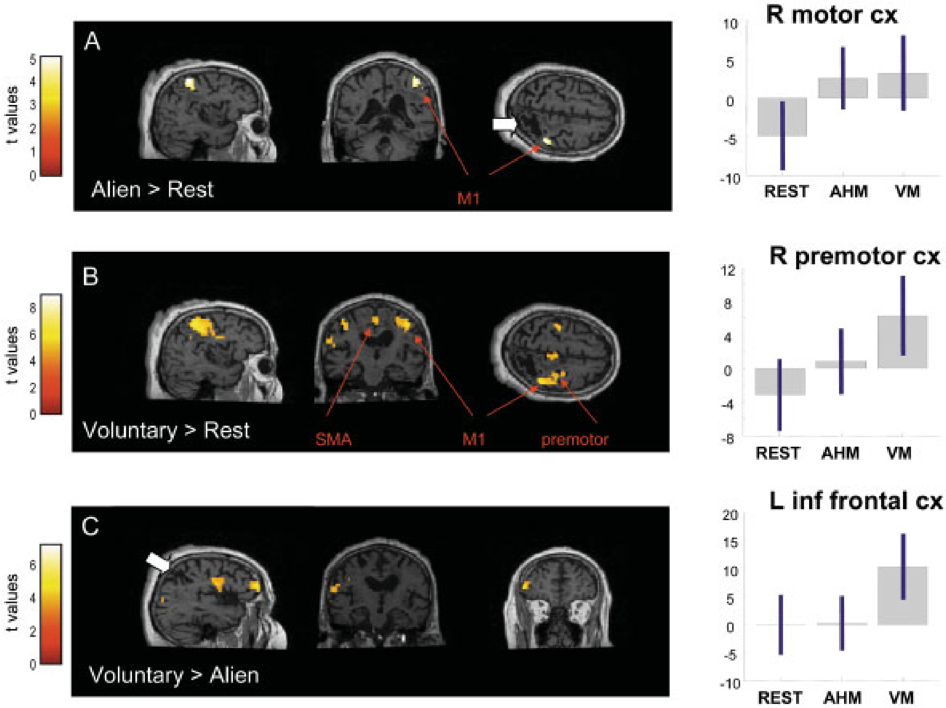

Fig 1. Brain areas activated in the first functional magnetic resonance imaging scan during (A) periods with alien movements of left hand (AHMs), relative to actual rest; (B) periods with voluntary movements (VMs) of left hand, relative to actual rest; or (C) periods with voluntary relative to alien movements of left hand. (right) Parameters of activity are plotted for regions of interest across these different conditions. Whereas M1 was activated similarly during voluntary or alien movements, right premotor and left prefrontal areas were activated selectively during voluntary movements. White arrows indicate right parietal lesion. SMA = supplementary motor area.

(via the instruction word "REST" continuously flashed on a screen at 0.5Hz, for 9 epochs/session, 20–40sec/epochs) or to perform short blocks of voluntary flexion-extension movements with his left hand (at a regular pace after the instruction "MOVE L" flashed at 0.5Hz on the screen, for 4 epochs/session, 20sec/epoch). Periods with rest instructions could contain either a real absence of movements or alien hand movements (AHMs), yielding three different conditions of interest: VMs, AHMs, and real rest (RR). These periods were subsequently analyzed in a standard block-design model in Statistical Parametric Mapping 2 (SPM2).[8]

The second experiment was a motor localizer scan, with periods of right or left hand movements alternating with rest (same design as described earlier, with three possible instructions "MOVE L," "MOVE R," or "REST"; 3, 4, and 7 epochs of 20 seconds, respectively).

All of the procedure was recorded by a MRI-compatible video camera, allowing us to monitor the patient's performance online, and then to use the recorded data to determine the precise onset times for the different movement conditions. Importantly, the patient could not see his hands during scanning. His arms and forearms were fixed on his body side by straps that allowed hand movements only, to minimize any other movements during the motor task.

Onsets of the different movement types were determined from the videos by three independent raters (with good agreement for >95% of video frames), with an additional measure for AHM intensity (mild or major, used as parametric regressor in SPM2). Overall, only 3.4% of the total time with VM instructions was not accompanied by correct performance, indicating that the patient complied well with our instructions. Periods with rest instructions were associated with AHM of major intensity, minor intensity, or RR in, respectively, 19.8, 47.2, and 33% of the time. During rest periods, the patient usually remained still for several seconds (mean, 18 seconds; range, 5–40 seconds) before AHM would start and then continue for variable durations (mean, 24 seconds; range, 5–42 seconds).

Magnetic Resonance Imaging Methods

Whole-brain fMRI was performed on a 1.5-Tesla Philips Intera system (Philips Medical Systems, Best, The Netherlands), using an echo-planar imaging gradient echo sequence (GRE) sequence (TR/TE/flip, 2 seconds/40 milliseconds/80 degrees; field of view, 250mm; matrix 128 × 128) with 20 contiguous 5mm axial slices (resolution, 1.95 × 1.95mm^2). Data were spatially realigned, smoothed (8mm Gaussian kernel), and analyzed on a voxel-by-voxel basis using SPM2 (Wellcome Department of Imaging Neuroscience, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm). The first study included three different conditions: VMs, AHMs, and RR, with an additional parametric regressor for AHM with marked versus mild intensity. The second (localizer) study included five conditions: right hand alone, left hand alone, right hand with left synkinesia, left AHM during rest, and RR. Realignment parameters of head motion were added as regressors of no interest to capture any residual movement-related artifacts. Each condition was modeled as a box-car block convolved with a canonical hemodynamic response function. The general linear model was used to generate parameter estimates of activity at each voxel, for each regressor in each session. Contrasts images were calculated by applying linear contrasts to parameter estimates of the corresponding regressors, with a statistical threshold of $p < 0.001$ uncorrected at the voxel level, cluster size < 10, and correction for multiple comparisons at $p < 0.05$ where indicated (Table). Activated regions in the patient were related to standard Montreal Neurological Institute brain coordinates by applying a normalization transformation on the nonnormalized coordinates of significant peaks.

Results

To identify regions activated during alien movements, we first contrasted periods with AHM versus RR. This demonstrated a selective activation of primary motor cortex (M1; $x, y, z = 43, -21, 28$; Z-score = 4.81; $p < 0.001$ at the voxel level; $p = 0.028$ family-wise error (FWE)-corrected; see Fig 1A). To assess whether M1 activity varied parametrically as a function of AHM intensity, we defined a region of interest in motor cortex based on the independent localizer scan and found a positive correlation of activation with the degree of AHM (peak at $x, y, z = 41, -8, 28$; $p = 0.023$).

VMs (VM minus RR) activated not only right M1 but also other motor regions including right premotor areas and SMA, plus selective increases in left prefrontal areas (including inferior frontal gyrus and frontal pole) and bilateral posterior parietal regions (see the Table; see Fig 1B). Bilateral activations in visual areas were also found, possibly because of greater attention to the task instructions on the screen (even though visual stimuli were similar across conditions except for the word cue). The contrast of VM versus AHM confirmed an increase in the same network of prefrontal and parietal areas, which were not activated during AHM (see Fig 1C). Importantly, the same contrast did not demonstrate any difference in M1 (Z-score = 1.49; $p = 0.07$, uncorrected voxel level).

Even at low threshold, we found no evidence for any brain area more activated during AHM than during both rest and VM (eg, alien > [voluntary + rest]). However, when comparing AHM relative to VM only, we found increased activity in ventral prefrontal areas only (see the Table). These areas were not specific to AHM, but were also more activated during RR and correspond to "default" resting state activity.[9,10]

Results from localizer scans in the second fMRI experiment testing VMs with either hand confirmed a robust activation in contralateral primary motor cortex and bilateral premotor areas during VMs (see the Table), for both left and right movements.[11] Remarkably, there was a perfect overlap between the peak of right-hemisphere M1 activity during voluntary left-hand movements and that found for AHMs in the first fMRI experiment (Fig 2). Furthermore, premotor areas, particularly left prefrontal regions, were activated by both right and left hand movements, suggesting an involvement in voluntary actions regardless of the hand used. Bilateral SMA regions were activated by left more than right movements, suggesting greater demands on motor preparation and control when moving the contralesional/affected hand.

The localizer fMRI scan also enabled us to replicate our findings for AHM. Again, we could compare periods with left AHM versus RR during this session: this confirmed a selective increase in right M1, with similar peak coordinates ($x, y, z = 45, -21, 28$; Z-score = 3.79; $p < 0.001$). Video observations from this session also demonstrated periods of abnormal left synkinesia (involuntary mirror left-hand movements occurring during voluntary right-hand movements), and additional analysis confirmed selective activation of right M1 during these periods with left synkinesia (ie, comparing right-hand movements with versus without left synkinesia).

Discussion

To our knowledge, these fMRI results show for the first time the neural correlates of AHM. A major novel finding is that AHM was associated with highly selective and isolated activation of contralateral M1. This contrasts with the extensive neural networks activated by VMs, and thus corroborates the patient's phenomenological experience of motor activity devoid of intentional planning. Strikingly, fMRI activity within M1 was identical during AHM and VM, for both intensity and anatomic peak. These results show that conscious and unconscious motor acts may recruit common neural substrates in M1, and that activity in primary motor cortex does not correlate with subjective experience of ownership for motor actions.

Table. **Activated areas during functional MRI**

Brain Areas	*x*, *y*, *z* Coordinates	*Z*-score
fMRI study 1: *Main alien hand experiment*		
AHM > RR		
R primary motor cortex	47, −26, 55	4.81
VM > RR		
R primary motor cortex	48, −29, 50	6.36
R parietal operculum	47, −23, 39	5.91
R premotor cortex	50, −9, 41	5.68
R superior frontal sulcus	39, 14, 40	4.58
R SMA	6, −13, 51	4.80
L premotor cortex	−44, −11, 45	5.67
L frontal pole	−52, 42, 3	5.82
L inferior frontal gyrus	−53, 13, 0	5.41
L superior frontal sulcus	58, −31, 1	5.08
ACC	3, 14, 25	4.93
R parietooccipital cortex	25, −77, 42	5.79
L parietooccipital cortex	−19, −78, 47	5.54
R occipital cortex	26, −92, 20	6.90
L occipital cortex	−20, −93, 20	6.09
VM > AHM		
R superior frontal sulcus	37, 14, 40	4.87
R premotor cortex	47, −7, 45	3.58
R SMA	4, −18, 62	3.11
L premotor cortex	−43, −13, 46	3.40
L frontal pole	−50, 50, −4	4.91
L inferior frontal gyrus	−69, −7, −16	5.89
L superior frontal gyrus	−13, 58, 29	4.61
R parietooccipital cortex	40, −66, 39	4.33
R inferior parietal cortex	61, −35, −3	4.23
L paretooccipital cortex	−24, −80, 37	4.72
L inferior parietal cortex	−64, −29, 10	4.32
AHM > VM		
R inferior frontal gyrus[a]	50, 23, −22	3.96
R orbitofrontal cortex[a]	18, 36, −25	3.73
fMRI study 2: *Motor localizer*		
Left VM > RR		
R primary motor cortex	47, −26, 55	5.58
R premotor cortex	48, −13, 47	4.38
R SMA	5, −5, 44	4.38
L premotor cortex	−48, −11, 45	5.04
L SMA	−5, −15, 42	4.83
L middle frontal gyrus	−43, 5, 32	4.72

Table. Activated areas during functional MRI Continued

Brain Areas	*x, y, z* Coordinates	*Z*-score
Right VM > RR		
L primary motor cortex	−40, −23, 58	4.03
L premotor cortex[a]	−46, −11, 45	3.39
L superior frontal gyrus[a]	−15, 55, 25	3.79
R premotor cortex[a]	44, −15, 47	3.41

All $p < 0.001$ at voxel level and $p < 0.05$ corrected for multiple comparisons. Coordinates are given according to Montreal Neurological Institute template, after transformation of activated peak locations from the patient into a normalized brain volume.
[a]Uncorrected multiple comparisons.
fMRI = functional magnetic resonance imaging; AHM = alien hand movements; RR = real rest; VM = voluntary movements; SMA = supplementary motor area; ACC = anterior cingulate cortex.

This circumscribed M1 activation might reflect a release from intentional planning systems subsequent to the parietal lesion, with spontaneous activity arising in the absence of goal-related selection of actions. Parietal damage may also explain that our patient was often unaware of his left-hand actions because of the lack of proprioceptive feedback in parietal cortex and/or deficient attention because of left spatial neglect.[12] These observations converge with electrophysiological data in AHS suggesting reduced inhibition of parietal cortex with increased somatosensory-evoked potentials[13] and abnormal SMA control with attenuation of Bereitschaftspotentials.[14] More specifically, our data confirm previous studies in brain-damaged patients that suggested that parietal cortex has a crucial role in generating conscious images of actions and maintaining internal motor representations,[15,16] which are necessary to the subjective sense of agency.[17] Thus, although M1 may code for limb movement planned by parietal systems, only activity in the latter (but not the former) may mediate conscious experience of motor intentions.[18] Importantly, we found no single brain area that was uniquely activated during AHS, indicating that involuntary ac-

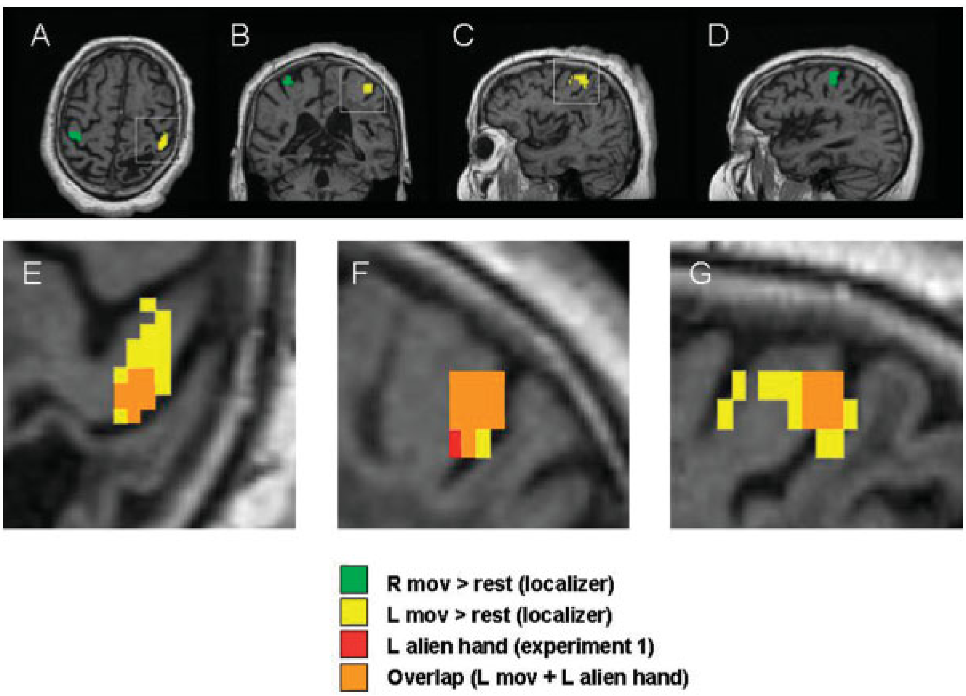

Fig 2. Cortical sites activated during the motor localizer scan, with peaks in (A–C) right M1 for left-hand voluntary movements relative to rest (yellow), and (A, B, D) left M1 for right-hand voluntary movements relative to rest (green). Enlarged views showing (E) axial, (F) coronal, and (G) sagittal sections of motor cortex (corresponding to brain sections shown in A, B, and C, respectively) demonstrate that cortical voxels activated during alien movement in the first functional magnetic resonance imaging scan (red) overlapped precisely with M1 voxels defined by the localizer scan (orange).

tivation of M1 was not driven by some other abnormal system.

In addition, our results support previous data from healthy subjects showing that VM is associated with distributed and bilateral activations beyond primary motor cortex (M1), including inferior frontal gyrus (BA6) and dorsolateral prefrontal cortex (BA9 and 46), preferentially on the left side, as well as bilateral anterior cingulate, SMA, and parietal areas.[11] Here we found that this bilateral network was activated by VM with either hand (right or left), but with left prefrontal areas being more strongly implicated than right prefrontal areas and specifically associated with voluntary relative to alien movements of the left hand. This preferential left prefrontal activation during left (and right) VM adds to previous proposals that the left (dominant) hemisphere may play a crucial role in guiding willed action,[19,20] although this asymmetry might also reflect some reorganization subsequent to right-hemisphere damage.

In conclusion, our imaging findings in this unique patient indicate that neural activity restricted to M1 may arise during unwilled or unconscious motor actions, and provide a direct demonstration that human motor pathways can function in the absence of motor awareness, as anticipated by some theories on internal models in the motor system.[1] These data open new perspectives for the comprehension of neurological and neuropsychiatric disorders associated with abnormal motor control or abnormal awareness of action, such as utilization behavior, phantom limb, anosognosia, or delusions of control in schizophrenia.[17]

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