Dysfunction of the Human Mirror Neuron System in Ideomotor Apraxia: Evidence from Mu Suppression

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Abstract

■ Stroke patients with ideomotor apraxia (IMA) have difficulties controlling voluntary motor actions, as clearly seen when asked to imitate simple gestures performed by the examiner. Despite extensive research, the neurophysiological mechanisms underlying failure to imitate gestures in IMA remain controversial. The aim of the current study was to explore the relationship between imitation failure in IMA and mirror neuron system (MNS) functioning. Mirror neurons were found to play a crucial role in movement imitation and in imitation-based motor learning. Their recruitment during movement observation and execution is signaled in EEG recordings by suppression of the lower (8–10 Hz) mu range. We examined the modulation of EEG in this range in stroke patients with left (n = 21) and right (n = 15) hemisphere damage during observation of video clips showing different manual movements. IMA severity was assessed by the DeRenzi standardized diagnostic test. Results showed that failure to imitate observed manual movements correlated with diminished mu suppression in patients with damage to the right inferior parietal lobule and in patients with damage to the right inferior frontal gyrus pars opercularis—areas where major components of the human MNS are assumed to reside. Voxel-based lesion symptom mapping revealed a significant impact on imitation capacity for the left inferior and superior parietal lobules and the left post central gyrus. Both left and right hemisphere damages were associated with imitation failure typical of IMA, yet a clear demonstration of relationship to the MNS was obtained only in the right hemisphere damage group. Suppression of the 8–10 Hz range was stronger in central compared with occipital sites, pointing to a dominant implication of mu rather than alpha rhythms. However, the suppression correlated with De Renzi's apraxia test scores not only in central but also in occipital sites, suggesting a multifactorial mechanism for IMA, with a possible impact for deranged visual attention (alpha suppression) beyond the effect of MNS damage (mu suppression). ■

INTRODUCTION

Apraxia is a disorder of motor control that is not attributed neither to motor deficits (e.g., paresis or dysmetria) nor to cognitive (e.g., inability to understand instructions) or sensory (e.g., visual) impairments (for reviews, see Goldenberg, 2009; Heilman & Rothi, 1993). Ideomotor apraxia (IMA) is probably the most prevalent and most studied type of apraxia. Patients with IMA show production errors in tasks of movement imitation and pantomime demonstration of common gestures. On imitation tasks, IMA patients often show preservative production, impaired temporal motor control (wrong sequencing and timing), and impaired spatial motor control (wrong organization of the movement in space; Haaland, Harrington, & Knight, 1999; Heilman & Rothi, 1993; for reviews, see Vanbellingen & Bohlhalter, 2011; Wheaton & Hallett, 2007).

Theories of apraxia have been dominated by Hugo Liepmann's classic model of the conversion of visual representations of movements into motor commands. According to this model, IMA is conceived as failure to this conversion. Stroke affecting the left parietal and frontal (premotor) areas is thought to be the most prevalent cause of the IMA syndrome (Goldenberg, 2009, 2014; Buxbaum, Kyle, & Menon, 2005; Weiss et al., 2001; Haaland, Harrington, & Knight, 2000). Over the years, the classic model has undergone changes (Goldenberg, 2009, 2014), and there is a continued debate concerning the precise neuroanatomical substrates of IMA (Buxbaum, Shapiro, & Coslett, 2014; for a review, see Petreska, Adriani, Blanke, & Billard, 2007) including debates on the involvement of right hemisphere damage in IMA (Schell, Suchan, Himmelbach, Haarmeier, & Borchers, 2014; Stamenova, Black, & Roy, 2012; Stamenova, Roy, & Black, 2010; Petreska et al., 2007; Heath, Roy, Black, & Westwood, 2001; Roy et al., 2000; Marchetti & Della Sala, 1997; Haaland & Flaherty, 1984).

Mirror neurons are a class of neurons that are active during both performance and observation of motor actions. This property was first demonstrated in cortical neurons of macaque monkeys, primarily in the ventral premotor cortex (F5) and around the anterior intraparietal sulcus (Fogassi et al., 2005; di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). More recently, a human analogue of the mirror neuron system (hMNS) has been suggested on the basis of functional brain imaging

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(fMRI; Fabbri-Destro & Rizzolatti, 2008; Morin & Grezes, 2008; Buccino, Lui, et al., 2004), TMS (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995), single-unit recording (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010), magnetoencephalography (Hari, 2006), and EEG (Pineda, 2005; Muthukumaraswamy, Johnson, & McNair, 2004; Cochin, Barthelemy, Roux, & Martineau, 1999).

The hMNS has been shown to reside in a network composed of the inferior frontal gyrus pars opercularis–ventral premotor cortex (IFGpo-PMv) and the anterior part of the inferior parietal lobule (aIPL). Adjacent areas in the temporal and parietal cortices also seem to contain neurons with mirror properties (Cross, Torrisi, Reynolds Losin, & Iacoboni, 2013; Molenberghs, Cunnington, & Mattingley, 2012; Keuken et al., 2011; Caspers, Zilles, Laird, & Eickhoff, 2010; Gazzola & Keysers, 2009; Filimon, Nelson, Hagler, & Sereno, 2007; Gazzola, Rizzolatti, Wicker, & Keysers, 2007; Grezes, Armony, Rowe, & Passingham, 2003). The extensive hMNS research has been motivated by the alleged importance of this system in a large variety of human abilities involving association between actions and their visual representations (for a review, see Rizzolatti & Sinigaglia, 2010). The focus in the current study is on the ability to imitate movements done by others, which is a prerequisite for the related ability of imitation-based motor learning (Celnik, Webster, Glasser, & Cohen, 2008; Stefan, Classen, Celnik, & Cohen, 2008; Celnik et al., 2006; Stefan et al., 2005; Buccino, Vogt, et al., 2004; Iacoboni et al., 1999; for reviews, see Iacoboni, 2005; Rizzolatti & Craighero, 2004).

The ability to imitate a given gesture is thought to be based on a direct activation of the corresponding neural networks underlying a motor gesture, upon observing the same gesture as it is done by another person (for reviews, see Rizzolatti & Sinigaglia, 2010; Brass & Heyes, 2005). Iacoboni et al. (1999) found significantly greater activation in "mirror areas" (the left IFGpo and the anterior part of the right parietal cortex) during imitation of finger movements, compared with mere observation of such movements or their execution under nonimitative conditions. Buccino, Vogt, et al. (2004) found that the basic circuit underlying learning by imitation of manual movements consists of the IFGpo-PMv and aIPL cortices, that is, the core structures of the hMNS. Coactivation shown in prefrontal (BA 46), superior-parietal, and rostral mesial cortical regions was thought to reflect control operations.

On the basis of the above findings concerning the hMNS role in movement imitation, we hypothesized that imitation failure in stroke patients, being a key feature of IMA (Wheaton & Hallett, 2007; Heilman & Rothi, 1993), involves hMNS dysfunction. Indeed, McGeoch, Brang, and Ramachandran (2007) already raised the idea that integrity of the MNS is crucial for normal limb praxis. Also, Pazzaglia, Smania, Corato, and Aglioti (2008) showed that apractic patients are impaired in their ability to judge whether familiar gestures are performed in a correct manner. This capacity to link between the perceptual and the motor components of an action is suggested to be attributed to the MNS (Rizzolatti & Sinigaglia, 2010).

Electrophysiological research of the hMNS focuses on the phenomenon of mu suppression. This is because of the dual characteristic of mu suppression, that is, its manifestation both during execution and during observation of biological movement (for a review, see Pineda, 2005). However, suppression of the 8–12 Hz band is not specific to activation of mirror mechanisms. It is evident, especially in posterior cortical areas, during nonspecific visual stimulation, showing sensitivity to the modulatory effects of attention, memory, and other task factors (Sauseng & Klimesch, 2008; Klimesch, Sauseng, & Hanslmayr, 2007; Klimesch, 1997). Because action observation inherently involves attentive focusing on visual targets, desynchronization of alpha rhythms, unrelated to mirror mechanisms, is likely to co-occur. There is evidence suggesting a different physiological meaning to different segments of the alpha range. Klimesch (1997) found that modulation of the upper alpha band is particularly sensitive to semantic memory demands, whereas modulation of the lower alpha band seems to reflect the effect of attentional processes. Recently, we have found that suppression occurring both during execution and observation of manual movement is a property of the lower (8–10 Hz) mu range, whereas the higher (10–12 Hz) range is suppressed mainly by execution and much less by observation of movement (Frenkel-Toledo, Bentin, Perry, Liebermann, & Soroker, 2013). In the same vein, Cochin et al. (1999) reported that both observation and execution of finger movements involved a decrease in the lower alpha band compared with resting conditions. These and other findings (see Frenkel-Toledo, Bentin, Perry, Liebermann, & Soroker, 2014; Perry et al., 2010; Marshall, Bouquet, Shipley, & Young, 2009) suggest that the activity of the presumed hMNS may be evident primarily in the lower mu range.

To test the relationship between failure to imitate gestures in IMA with hMNS dysfunction, we examined 36 stroke patients and correlated their imitation performance with the magnitude of mu suppression shown in EEG recordings done during observation of manual activities. Showing that mu suppression in the lower range during action observation is attenuated in IMA patients as compared with non-IMA patients is expected to support a linkage between apraxia and dysfunction of the hMNS, especially if the severity of the apraxic disorder is shown to correlate negatively with the magnitude of mu suppression.

METHODS

Participants

Forty-one first-incident stroke patients (24 male) ranging in age from 24 to 81 years (mean ± *SD*: 57.6 ± 13.2 years) participated in this study. Patients were

recruited during their hospitalization at the Loewenstein Rehabilitation Hospital, Ra'anana, Israel. Upon admission to the study, the time after stroke onset ranged between 23 and 132 days (58.7 ± 29.4 days). Patients were included in the study only if they did not suffer from psychiatric or prior neurological disorders, they had normal or corrected-to-normal visual acuity, and their language and cognitive status enabled comprehension of the task requirements. All but one participant were right-handed. The patients signed an informed consent approved by the institutional ethics review board of the Loewenstein Rehabilitation Hospital and the Tel-Aviv University. Many of the patients participated in a previous study (Frenkel-Toledo et al., 2014). Three patients had to be excluded from the analysis because of excessive amount of artifacts in their EEG (1 man aged 60 and 2 women aged 65 and 63), and two additional patients were excluded due to refusal to participate in the entire experiment (2 men aged 73 and 67). Hence, the reported results are based on 36 participants; 21 patients with left hemisphere damage (LHD) and 15 patients with right hemisphere damage (RHD).

Apraxia was reported previously primarily in left stroke patients and seldom in right stroke patients (Vanbellingen & Bohlhalter, 2011; Petreska et al., 2007). Therefore, our research investigated LHD and RHD patients, separately. The LHD sample included 14 stroke patients with IMA (8 men) ranging in age from 26 to 81 years (61.4 ± 13.3) and 7 stroke patients without IMA (4 men), ranging in age from 24 to 57 years (45.7 ± 12.1). Time after stroke onset upon admission to the study ranged between 24–112 days for patients with IMA and 27–105 days for patients without IMA (59.9 ± 26 days and 44.9 ± 27.2 days, respectively). The RHD sample included 11 stroke patients with IMA (7 men), ranging in age from 43 to 71 years (61.1 ± 8.1) and 4 stroke patients without IMA (2 men), ranging in age from 24 to 76 years (48.8 ± 21.4). Time after stroke onset upon admission to the study ranged between 31–132 days for the patients with IMA and 15–82 days for the patients without IMA (73.7 ± 29.4 days and 37.3 ± 30.4 days, respectively). Diagnosis of IMA was carried out using De Renzi's (De Renzi et al., 1980) apraxia test (explained in the following section). The mean score ranged from 39 to 67 (57.1 ± 9.0) and from 39 to 65 (55.3 ± 8.5) in left IMA and right IMA patients, respectively. In the LHD group, the IMA patients were significantly older than non-IMA patients ($p = .017$) but did not differ with respect to gender ($p > 1.0$). In the RHD sample, the IMA patients were not statistically different from the non-IMA patients with respect to age and gender ($p > .1$). The demographic and clinical data of the patients are described in Table 1.

Two subgroups of IMA patients were of special interest—those with lesions involving the IPL and those with damage to the IFGpo (i.e., the cortical regions where the major components of the hMNS are assumed to reside; Rizzolatti & Sinigaglia, 2010). The subgroup of patients with IPL damage included five stroke patients (1 man) with damage in the left IPL, ranging in age from 43 to 81 years (65 ± 13.8), and five stroke patients (3 men) with damage in the right IPL, ranging in age from 56 to 76 years (67 ± 7.4). Time after stroke onset upon admission to the study ranged between 24–49 days for the left parietal patients and 71–132 days for the right parietal patients (39 ± 9.8 days and 93.8 ± 23.1 days, respectively). All five patients in the left IPL group and four of five patients in the right IPL group were diagnosed as having IMA according to De Renzi's apraxia test. The subgroup of patients with IFG lesion included seven stroke patients (4 men) with damage in the left IFG, ranging in age from 24 to 70 years (52.3 ± 17.3), and seven stroke patients (6 male) with damage in the right IFG, ranging in age from 43 to 71 years (62.1 ± 9.6). Time after stroke onset upon admission to the study ranged between 31–105 days for the left frontal patients and 40–132 days for the right frontal patients (69.9 ± 28.8 days and 86.3 ± 27.9 days, respectively). Five of the seven patients in the left IFG group and all seven patients in the right IFG group were diagnosed as having IMA according to De Renzi's apraxia test.

Clinical Examination and Apraxia Testing

The standardized Fugl-Meyer test (Gladstone, Danells, & Black, 2002; Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) was used for evaluation of the motor ability of the hemiparetic upper limb. IMA was assessed using De Renzi's apraxia test (Butler, 2002; De Renzi, Motti, & Nichelli, 1980), where patients are asked to imitate symbolic and nonsymbolic finger movements (12 items) and hand/arm movements (12 items). Each item is scored on a 4-point ordinal scale (0-1-2-3). The maximal score is 72, and the cutoff score is 68 (patients were characterized as exhibiting IMA if they scored below the cutoff). Butler (2002) compared four commonly used clinical tests for diagnosis of apraxia and found that this test was the most sensitive and reliable. As IMA affects both hands, scoring was based on testing performance of the noninvolved hand, such that it was not affected by interpersonal variance in the severity of spasticity and paresis affecting the involved hand. All tests were delivered by the same physical therapist.

Action Observation

Participants were examined in the following conditions:

(a) *Rest:* eyes closed and blindfolded (to assure minimal eye muscle contraction and complete darkness);
(b) *Baseline:* observing a nonbiological movement—a video clip showing a rolling ball on a table;
(c) *Right Egocentric:* observing a video clip showing reaching and grasping an object with the right hand observed from an egocentric viewpoint (the participant sees the actor from behind);

Table 1. Patients' Demographic and Clinical Data

Patient	Age/ Sex	Lesion Side	IPL Damage (%)	IFGpo Damage (%)	Lesion Type	TAO	VFD	Neglect (SC-/54)	Sensation (FM-/12)	Motor Ability (FM-/66)	De Renzi Test (−/72) NUL
FAM*	65/M	R		47.4	I	81	–/e	53	10	4	42
UBC	67/M	R		1.6	I	40	–	54	12	4	65
AA	50/F	R			I	23	–	54	2	34	71
SK	64/M	R			H	66	–/e	49	2	31	56
AP	76/F	R	1.3		I	82	–	54	12	43	69
AM	63/F	R			I	43	–	54	12	21	65
YH	45/M	R			I	15	–	54	12	17	72
AN	53/F	R			I	67	–	29	8	17	39
YS	67/M	R	11.7	12.2	I/H	71	–	53	0	4	58
YM	56/F	R	20.4	66.5	H	132	–/e	54	4	31	60
SAK	43/M	R		13.4	H	96	–/e	54	1	1	49
AH	23/M	R			I	29	–	54	12	66	72
AAD	57/F	R			H	31	–	54	8	5	58
YL	71/M	R	31.7	0.2	H	89	–	53	4	20	56
AM	66/M	R	49.5	16.9	I	95	–/e	51	12	64	65
RH	42/M	L			I	27	–	54	10	53	69
AH	24/F	L		1.5	I	31	–	54	12	9	68
MB	26/F	L			I	112	–	54	12	36	67
GA	71/M	L			I/H	52	–	53	10	44	50
YY	57/M	L			I	36	–	54	12	32	69
SCV	39/F	L		2.6	H	105	–	54	8	57	68
GG	64/M	L			I	58	–	54	12	59	67
AK	55/M	L			I	33	–	54	12	15	71
IO	60/M	L		15.8	I	93	–	54	12	47	64
BS	61/M	L		4.5	I	71	–	53	12	14	58
DE	62/M	L			H	59	–	54	12	0	65
YH	55/M	L			H	73	–	54	12	27	67
DD	46/M	L			I	36	–	54	12	64	68
YB	65/F	L			I	31	–	54	12	32	50
NS	65/F	L	65.9		I	42	–	54	5	41	39
ED	57/F	L			H	46	–	54	12	13	69
SB	43/F	L	16.8	75.7	H	49	–	54	10	18	54
TK	67/F	L	64.7		I	24	–	54	11	60	58
IB	70/M	L		89.6	I	95	–	54	8	50	62
SH	81/F	L	4.3		I	35	–/e	54	12	58	55
DE	69/M	L	12.0	1.5	H	45	–	45	8	4	44

H = hemorrhagic stroke; I = ischemic stroke; I/H = ischemic with hemorrhagic transformation; IPL damage = % of inferior parietal lobule damaged by the stroke (see Methods for the exact definition of the region); TAO = time after stroke onset (days); VFD = visual field defect (− = no VFD; −/e = extinction upon bilateral simultaneous stimulation but no VFD); SC = Star Cancellation subtest of the Behavioral Inattention Test for neglect (SC cutoff for normality = 52, maximal score = 54; Halligan, Wilson, & Cockburn, 1990); FM = Fugl-Meyer test (Gladstone et al., 2002; Fugl-Meyer et al., 1975); De Renzi's apraxia test (Butler, 2002; De Renzi et al., 1980) = maximal score = 72, cutoff score for normality = 68, performance with the noninvolved upper limb; HUL = hemiparetic upper limb; NUL = noninvolved upper limb.

*This patient was the only left-handed individual in the group.

(d) *Left Egocentric:* observing a video clip showing reaching and grasping an object with the left hand observed from an egocentric viewpoint;
(e) *Right Allocentric:* observing a video clip showing reaching and grasping an object with the right hand observed from an allocentric viewpoint (the participant faces the actor); and
(f) *Left Allocentric:* observing a video clip showing reaching and grasping an object with the left hand observed from an allocentric viewpoint.

The experimental protocol is similar to the protocol we used in a recent study (Frenkel-Toledo et al., 2013) where we explored the effect of action observation from different viewpoints on mu suppression. Because viewpoint and hand effects are irrelevant to the current research question, the egocentric and allocentric viewpoint perspectives and the right and left hands were collapsed. Also, the *Rest* condition, which was used as an additional baseline in the previous study (Frenkel-Toledo et al., 2013), is irrelevant for the current research question and, therefore, was not analyzed.

E-Prime (Psychological Software Tools Inc., V2.0, Sharpsburg, PA) was used for stimulus presentation and experimental control. Each condition lasted 100 sec. The *Rest* condition (a) was always first in order to prevent possible carry-over effects from the active blocks into the rest condition. The order of the five movement observation conditions (b–f) was fully randomized across participants. In each of the five movement observation conditions, the participants observed 84 consecutive video clips (1.2 sec each) presented in random order. The video clips in each of the biological movement observation conditions (c–f) showed six manual reaching and grasping movements with different objects either with a precision grip ("narrow-grasping") or with a power grasp ("wide-grasping"). Each of these conditions was composed of two blocks. The video clips in one block presented mainly wide-grasping, whereas those in the other block presented mainly narrow-grasping movements. In the nonbiological movement condition (b), a tennis ball rolled on a table from the bottom to the top of the screen or vice versa (i.e., out in the radial direction in table coordinates).

To ensure that participants remained focused on the screen throughout the experiment, they were asked to engage in a monitoring task (Perry & Bentin, 2009). The task in the nonbiological movement condition consisted of counting silently the number of times the rolling ball stopped before reaching the end of the screen. In the wide-grasping observation condition, the task was to count silently the number of four to six narrow-grasping movements randomly occurring. On the contrary, during the presentation of the other block, the task consisted of counting four to six wide-grasping movements also randomly occurring. Upon completion of each observation block, the participants were asked to report how many times the task stimulus appeared (the participants received a computerized feedback). The participants were instructed to avoid moving during the passive video clip observation. The video clips were presented on a computer monitor at approximately 70 cm in front of the participant's eyes.

Electroencephalography during Action Observation

The EEG analog signal was recorded continuously via 32 Ag–AgCl pin-type active electrodes (except for two patients form the LHD group who used a 64-channel cap) mounted on an elastic cap (Biosemi, Amsterdam, the Netherlands, www.biosemi.com/headcap.htm) according to the extended 10–20 method of electrode placing and from two additional electrodes placed at the right and left mastoids. During recording, all electrodes were referenced to a common mode sense electrode between Cz and C3 and subsequently were re-referenced digitally (see data processing sections below). Eye movements as well as eye blinks were monitored using bipolar horizontal and vertical EOGs via two pairs of electrodes. One pair was attached to the external canthi, and the other pair was attached to the infraorbital and supraorbital regions of the right eye. Both EEG and EOG were sampled at 1024 Hz, digitally amplified and low-pass filtered at 268 Hz using a Biosemi Active II system.

Preprocessing

Data were analyzed offline using Brain Vision Analyzer software (Brain Products, Gilching, Germany, www.brainproducts.com). Raw EEG data were low-pass filtered offline at 30 Hz and high-pass filtered at 0.5 Hz (Butterworth filter, 24 dB) and re-referenced offline to the digital average of the two mastoids. Eye movements and blinks were corrected using independent component analysis (Jung et al., 2000). Remaining artifacts exceeding ± 100 μV in amplitude were detected, and the 300-msec epochs around these artifacts were excluded from the analysis. Each EEG data segment began at the onset of the video clip. For each such segment, the integrated power in 8–10 Hz frequency band was computed using a fast Fourier transform, at 0.5-Hz intervals (using a Hanning window).

EEG Suppression Analysis

The first 10 sec of each block of data were excluded from the analysis to eliminate the possibility of attentional transients due to initiation of the stimulus. The remaining time was segmented in epochs of 1150 msec (excluding the times where the clips showing the target stimulus for the silent counting task were presented). Mu suppression was calculated as the ratio of the power during the biological movement observation condition relative to the power during the nonbiological movement condition.

This ratio (rather than simple subtraction) was used to control for the variability in absolute EEG power resulting from individual differences such as scalp thickness and electrode impedance (Doppelmayr, Klimesch, Pachinger, & Ripper, 1998; see also Pineda & Oberman, 2006). Furthermore, because ratio scores do not distribute normally, we used a log (ln) transform of the ratio as the dependent variable in the EEG suppression analysis. A log ratio lower than zero indicates suppression, whereas a value of zero indicates no suppression and values greater than zero indicate event-related synchronization, which manifests as an increase in power relative to baseline.

Suppression indices were computed primarily at central sites C3 and C4, where the maximal manifestation of the hMNS activity has been reported (Frenkel-Toledo et al., 2013; Pineda, 2005). It should be noted that alpha and mu rhythms fall within the same EEG frequency range. Alpha rhythms are desynchronized in association with visual stimulation and while processing information that requires attention and memory, especially over the occipital cortex (Klimesch et al., 2007; Klimesch, 1997; Khulman, 1978). Mu rhythms are typically desynchronized during execution of movement, most prominently over the sensorimotor cortex (for a review, see Pineda, 2005). Several studies found a widespread suppression across the scalp and even a greater suppression at occipital sites compared with central sites during action observation (Perry, Stein, & Bentin, 2011; Perry & Bentin, 2009; Perry et al., 2010). In contrast, other studies found greater mu suppression at central sites (Frenkel-Toledo et al., 2013; Oberman, Ramachandran, & Pineda, 2008; Oberman et al., 2005). Because the cortical distribution of suppression patterns during action observation showed inconsistencies, suppression indices were computed at additional sites across the scalp: frontal F3, F4, parietal P3, P4, and occipital O1 and O2.

Lesion Analysis

Lesion analyses were conducted to describe the lesion profiles of the IMA and non-IMA stroke patients and to identify stroke patients with damage in predetermined ROIs. Two ROIs, IPL and IFG, were examined because these cortical regions are thought to be key components of the hMNS (Rizzolatti & Sinigaglia, 2010) and they also play a key role in praxis (Chaminade, Meltzoff, & Decety, 2005; Muhlau et al., 2005). Follow-up CT scans, dating on average 6–7 weeks poststroke onset, were examined to ensure that lesion boundaries were clear and traceable and that the CT presented a stable pattern of tissue damage without a mass effect from residual edema. This procedure was carried out to eliminate lesion boundary delineation errors due to temporary density changes reflecting perilesional edema, as seen in the post-acute stage. Lesion analyses were performed with the Analysis of Brain Lesions (ABLe) module implemented in MEDx software (Medical-Numerics, Sterling, VA). Lesion delineation was made manually on the digitized CTs. ABLe characterizes brain lesions in MRI and CT scans of the adult human brain by spatially normalizing the lesioned brain into Talairach space using the Montreal Neurological Institute (MNI) template. It reports tissue damage in the normalized brain using an interface to the Talairach Daemon (San Antonio, TX), Automated Anatomical Labeling (AAL) atlas, Volume Occupancy Talairach Labels atlas, or the White Matter atlas (Solomon, Raymont, Braun, Butman, & Grafmanc, 2007; Tzourio-Mazoyer et al., 2002; Lancaster et al., 2000). Finally, a quantification of amount of tissue damage within each structure/region of the atlas was obtained (described earlier in Haramati, Soroker, Dudai, & Levy, 2008).

In the current study, tissue damage in the normalized brain was reported using the interface to the AAL atlas (Tzourio-Mazoyer et al., 2002). Lesion data from three patients were excluded: one patient from the RHD group showed a small lesion confined to a white matter region, which is not included in the parcellation of the AAL atlas; in the other two patients (one patient from each of the LHD and RHD groups), the CT failed to demonstrate a clear parenchymal damage. Registration accuracy of the scans to the MNI template ranged from 93.6% to 95.8% (94.6 ± 0.5; 94.7 ± 0.5 and 94.6 ± 0.4 in LHD and RHD patients, respectively).

In the subgroup of 10 stroke patients with IPL damage, registration accuracy of the scans to the MNI template ranged from 94.1% to 95.8% (94.7 ± 0.51; 94.9 ± 0.6 and 94.4 ± 0.2 in LHD and RHD patients, respectively). The ROI examined in the current study was the cortical region termed P2 in the AAL atlas (Tzourio-Mazoyer et al., 2002), which is the part of the IPL cortex delineated by the postcentral sulcus (anteriorly), the anterior part of the intraparietal sulcus (superiorly), the supramarginal gyrus (inferiorly), and the angular gyrus (posteriorly).

In the subgroup of 14 stroke patients with IFG damage, registration accuracy of the scans to the MNI template ranged from 94.1% to 95.8% (94.7 ± 0.46; 94.8 ± 0.53 and 94.5 ± 0.34 in LHD and RHD patients, respectively). Table 1 presents the alphanumeric output of the normalization procedure and the apraxia score for the patients. The extent of damage in IPL and IFG (% voxels involved in that region) is shown for each patient in AAL atlas regions involved in at least one patient.

Voxel-based lesion symptom mapping (VLSM; Bates et al., 2003) is used to identify voxels of the normalized brain where damage has a significant impact on tested behaviors. Voxel-by-voxel analysis calculates the statistical significance of the difference (using *t* tests) in performance between participants with damage in a given voxel and participants who are not damaged in that voxel. Thus, it discriminates between voxels where the damage affects the tested behavior and voxels where damage does not affect that behavior. To assess the contribution of a given voxel using VLSM, the requirement is that at least three participants have damage to that particular

voxel (Haramati et al., 2008). To correct for multiple comparisons, voxels with values exceeding a false discovery rate (FDR) threshold of $p < .05$ were considered significant (Genovese, Lazar, & Nichols, 2002).

RESULTS

LHD and RHD Patient Groups

Spatial Distribution of Suppression

Because action observation-related suppression was reported previously, but inconsistently, at occipital sites (Frenkel-Toledo et al., 2013; Perry et al., 2010, 2011; Perry & Bentin, 2009; Oberman et al., 2005, 2008), we compared the magnitude of desynchronization between central and occipital sites. Suppression index (averaged across the different viewing perspectives and hands; see Methods) was analyzed using a two-way ANOVA with repeated measures. The within-subject factors were Site (two levels: central, occipital) and Hemisphere (two levels: affected, unaffected). A Lesion Side factor was added as between-subject factors in the ANOVA. The significance level for all statistical analyses was set at $p < .05$. Lesion side had no significant effect on suppression indices [$F(1, 34) = 3.64$, $MSE = 0.108$, $p = .065$]. The only main effect that reached significance was Site [$F(1, 34) = 4.72$, $MSE = 0.013$, $p = .037$]. The significant main effect of Site emerged from a greater suppression at the central (mean = −0.059) compared with the occipital site (mean = −0.018). There were no other significant effects in this analysis.

Additionally, scalp distributions of suppression in the 8–10 Hz in the different observation conditions (collapsed over Hands and Viewpoints) were conducted separately for LHD and RHD patient groups (Figure 1). As can be seen, suppression was stronger at central than at occipital sites.

The Effect of Total Hemispheric Volume Loss on Mu Suppression

To rule out the possibility that the magnitude of mu suppression was influenced by lesioned brain tissue rather than lesion in the hMNS, quantitative measures of normalized lesion data (see Methods) were used to assess the impact of total hemispheric volume loss on the magnitude of mu suppression in the 8–10 Hz at central sites during action observation. The significance level for all statistical analyses was set at $p < .05$. No significant correlations were found between volume loss and mu suppression, neither in the affected nor in the unaffected hemisphere in the RHD (affected hemisphere: $r = .055$, $p = .858$; unaffected hemisphere: $r = .116$, $p = .707$) and LHD groups (affected hemisphere: $r = .39$, $p = .089$; unaffected hemisphere: $r = .19$, $p = .937$).

Total Lesion Extent in IMA and Non-IMA Patients

Total lesion volume of the 20 LHD patients ranged 1.4–111.6 cc (28.1 ± 27.1 cc). Lesion volume ranged 1.4–111.6 cc (29.8 ± 31.4 cc) and 2.2–40.6 cc (24.2 ± 13.9 cc) in the left IMA and left non-IMA patients, respectively. In the 13 RHD patients, lesion volume ranged 1.0–162.4 cc (48.4 ± 48.9 cc). Lesion volume ranged 1.2–162.4 cc (61.3 ± 48.8 cc) and 1–12.4 cc (5.7 ± 6.0 cc) in the right IMA and non-IMA patients, respectively. Figure 2 is a graphical output of the normalization procedure depicting each patient's lesion on a Damasio and Damasio (1989) set of standard templates (only lesion-containing slices are shown).

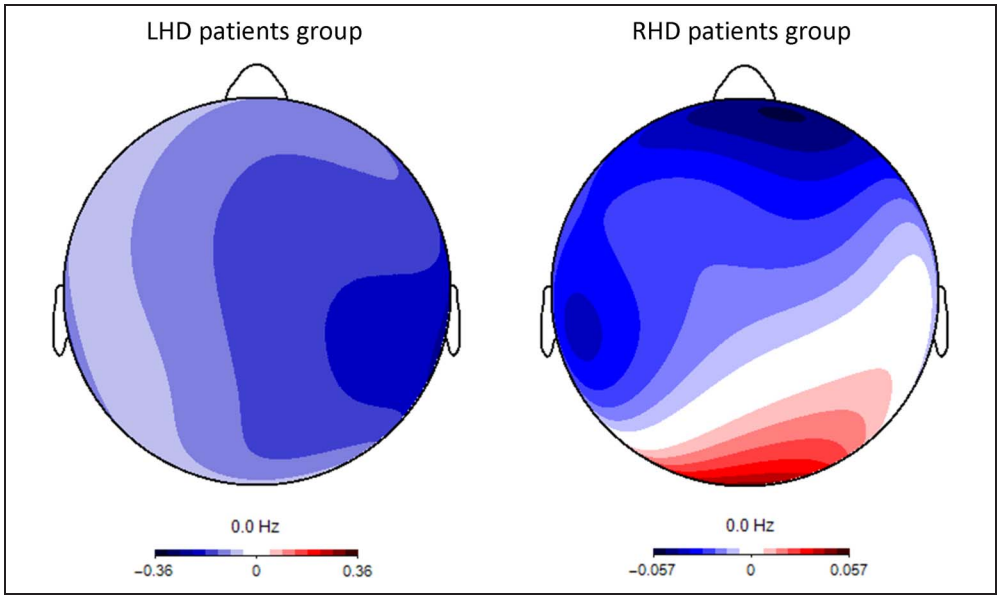

Figure 1. Scalp distribution of suppression. The scalp distribution of suppression in the observation conditions (averaged across hand and viewpoint perspectives) in the 8–10 Hz, presented separately in LHD and RHD patient groups. Note that suppression was stronger at central than at occipital sites. In each scalp distribution, the right hemisphere is on the reader's right.

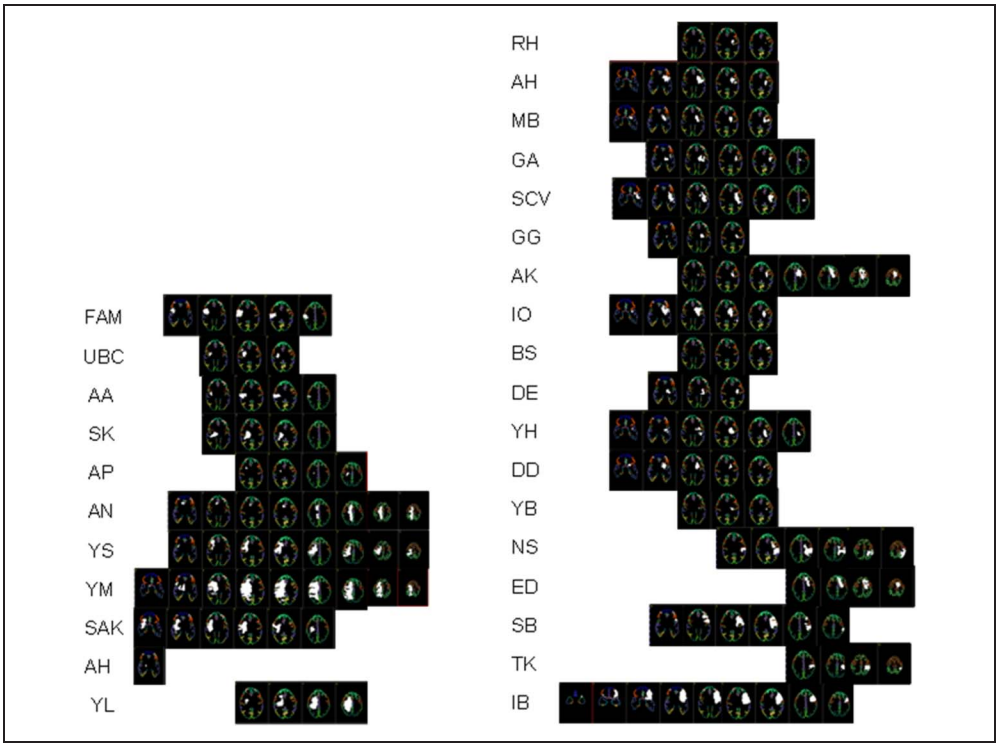

Figure 2. Normalized lesion data. Each patient's lesion marked on arrays of 11 standard templates (Damasio & Damasio, 1989). Displays follow neurological conventions, that is, right-sided damage displayed on the left and left-sided damage displayed on the right side (one patient with right cerebellar stroke is not shown here). Only CT slices that present brain damage are shown.

Mu Suppression in IMA versus Non-IMA Patients

We compared the magnitude of low mu suppression in IMA and non-IMA stroke patients, as measured in central sites during observation of manual movements (collapsed across hands and viewpoints, because these factors were not relevant for the current question of concern). Since in a previous study (Frenkel-Toledo et al., 2014), stroke patients showed less suppression in the affected hemisphere as compared with the unaffected hemisphere, we examined the differences in each hemisphere. Comparisons were made separately for the LHD and RHD patient groups. The significance level was set at $p < .05$. Because of the small number of IMA and non-IMA patients in both LHD and RHD patient groups (see Participants section in Methods) and the use of ordinal apraxia test scores, we used the Mann–Whitney statistical test. Mu suppression did not differ between IMA and non-IMA patients, both at the affected and unaffected hemispheres, neither in the LHD nor in the RHD patient groups.

Correlation between Mu Suppression and Apraxia Score in IMA Patients

Table 2 presents the Spearman's rho correlation coefficients between the magnitude of mu suppression at the lower range as recorded in central sites (C3, C4), frontal sites (F3, F4), parietal sites (P3, P4), and occipital sites (O1, O2) and De Renzi's apraxia test scores in LHD and RHD IMA patients (calculated separately for the affected and unaffected hemispheres). Because mu suppression is expressed in negative values, a negative correlation means that apraxia of lesser severity (higher test score) correlates with mu suppression of larger magnitude (more negative). The correlation analysis was conducted using $p < .05$ for significance and an FDR-corrected threshold of pFDR $< .05$ for significance.

As can be seen in Table 2, in the left and right IMA group, De Renzi's apraxia test scores did not significantly correlate with the magnitude of mu suppression for both the affected and unaffected hemispheres.

VLSM Analysis

To investigate whether there are particular brain regions that affect both imitation capacity (De Renzi's apraxia test scores) and mu suppression (8–10 Hz, recorded from C3 and C4 electrodes), we aimed to perform a conjunction VLSM analysis (Buxbaum et al., 2014; Bates et al., 2003; see Methods) for (a) mu suppression indices obtained from each hemisphere and (b) the apraxia test scores, separately for the LHD ($n = 20$) and RHD ($n = 13$) groups. First, lesion density overlap maps were created by overlaying the individual normalized lesion maps of LHD and RHD patient groups. The maps showed that much of the fronto-parietal area of interest lacks the minimum requirement of three subjects with overlapping lesions (Figure 3). Therefore, the basic requirement for VLSM analysis was not fulfilled for much of the voxels in our ROIs. Having this caveat in mind, we still performed VLSM analyses and found significant (FDR-corrected) results only with respect to De Renzi's apraxia test in the LHD patient group. The analysis identified one cluster of

Table 2. Correlation between DeRenzi's Apraxia Test Score and the Magnitude of Mu Suppression in IMA Patients with LHD and RHD

			p	
		Spearman's Rho	*Uncorrected*	*pFDR < .05*
LHD (n = 14)				
Central sites	Affected H	−0.502	.067	.536
	Unaffected H	0.055	.851	.892
Frontal sites	Affected H	−0.259	.372	.892
	Unaffected H	−0.40	.892	.892
Parietal sites	Affected H	−0.128	.662	.892
	Unaffected H	−0.093	.752	.892
Occipital sites	Affected H	0.252	.384	.892
	Unaffected H	−0.177	.545	.892
RHD (n = 11)				
Central sites	Affected H	−0.697	**.017**	.084
	Unaffected H	−0.578	.063	.084
Frontal sites	Affected H	−0.615	**.044**	.084
	Unaffected H	0.509	.110	.110
Parietal sites	Affected H	−0.628	**.038**	.084
	Unaffected H	−0.596	.053	.084
Occipital sites	Affected H	−0.546	.082	.094
	Unaffected H	−0.647	**.031**	.084

Significance represented in **bold**.

cortical voxels associated with reduced imitation capacity (centroid [in Talairach coordinates] at −32, −24, 34), involving the left IPL (230 voxels), left superior parietal lobule (46 voxels), and left post central gyrus (120 voxels). Because the initial VLSM did not reveal a significant impact on the magnitude of mu suppression, it was impossible to proceed with the intended conjunction analysis. It should be noted that additional VLSM analyses conducted for suppression indices obtained from frontal F3, F4, parietal P3, P4, and occipital O1, O2 sites also did not yield significant results.

Subgroups of LHD and RHD IMA Patients

Lesion Extent in the Subgroup of Patients with IPL Damage

Total lesion volume in the five patients with left IPL damage ranged from 13–69 cc (40 ± 24 cc). In the five patients

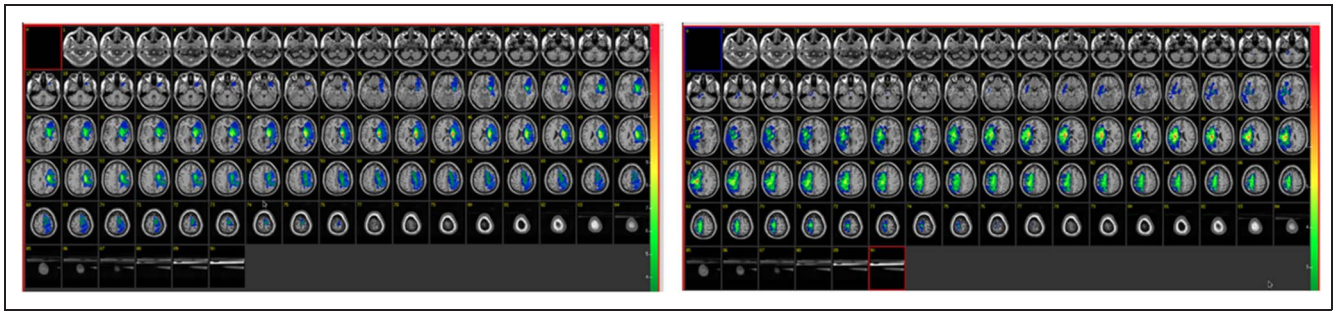

Figure 3. Lesion density map for the LHD and RHD groups. Color indicates the number of overlapping lesions at each voxel. Red indicates more participants, and blue indicates fewer participants. The analysis was restricted to a minimum overlap of three patients in a given voxel. In each slice, the right hemisphere is on the reader's left.

with right parietal damage, total lesion volume ranged from 4–162 cc (88 ± 56 cc). Lesion extent within the inferior parietal cortex (area labeled P2 in the AAL atlas, explained in the Methods section) ranged between 4.3% and 65.9% (32.7 ± 30.1%) in the left parietal group and between 1.3% and 49.5% in the right parietal group (22.9 ± 18.6%). The extent of damage to the inferior parietal cortex in each patient is depicted in Table 1. The graphical output of the normalization procedure depicting each patient's lesion on a Damasio and Damasio (1989) set of standard templates (only lesion-containing slices are shown) is included in Figure 2 (left IPL group, patients: NS, SB, TK, SH, and DE; right IPL group, patients: AP, YS, YM, YL, and AM).

Correlation between Mu Suppression and Apraxia Score in the Subgroup of IMA Patients with IPL Damage

Table 3 presents the Spearman's rho correlation coefficients between the magnitude of suppression at the lower mu range (8–10 Hz), as recorded in central sites (C3, C4), frontal sites (F3, F4), parietal sites (P3, P4), and occipital sites (O1, O2), and De Renzi's apraxia test scores in IMA patients with left IPL and right IPL damage (calculated separately for the affected and unaffected hemispheres). As can be seen in Table 3, De Renzi's apraxia test scores correlated significantly with the magnitude of mu suppression in the affected hemisphere at frontal and central sites in the right IPL-damaged patients only. The magnitude of suppression in the 8–10 Hz in the unaffected hemisphere at occipital sites correlated significantly with De Renzi's apraxia test scores as well.

Lesion Extent in the Subgroup of Patients with IFGpo Damage

Total lesion volume in seven patients with left frontal damage ranged from 1.4–111.6 cc (47.8 ± 34.8 cc). In the seven patients with right frontal damage, total lesion volume ranged 10.9–162.4 cc (78 ± 48.4 cc). Lesion extent within the inferior frontal-opercular cortex ranged between 1.5% and 86.9% in the left frontal group (27.3 ± 38.3%) and between 1.6% and 66.5% (22.6 ± 24.9%) in the right frontal groups. The extent of damage to the inferior frontal cortex in each patient is depicted in Table 1. The graphical output of the normalization procedure

Table 3. Correlation between DeRenzi's Apraxia Test Score and the Magnitude of Mu Suppression in the Subgroup of IMA Patients with Left and Right IPL Damage

			p	
		Spearman's Rho	*Uncorrected*	*pFDR < .05*
LHD (n = 5)				
Central sites	Affected H	−0.9	**.037**	.296
	Unaffected H	−0.5	.391	.626
Frontal sites	Affected H	−0.3	.624	.713
	Unaffected H	0.1	.873	.873
Parietal sites	Affected H	−0.7	.188	.570
	Unaffected H	−0.6	.285	.570
Occipital sites	Affected H	0.6	.285	.570
	Unaffected H	−0.4	.505	.673
RHD (n = 4)				
Central sites	Affected H	−1.0	**.01**	**.027**
	Unaffected H	−0.8	.2	.200
Frontal sites	Affected H	−1.0	**.01**	**.027**
	Unaffected H	−0.8	.2	.200
Parietal sites	Affected H	−0.8	.2	.200
	Unaffected H	−0.8	.2	.200
Occipital sites	Affected H	−0.8	.2	.200
	Unaffected H	−1.0	**.01**	**.027**

Significance represented in **bold**.

Table 4. Correlation between DeRenzi's Apraxia Test Score and the Magnitude of Mu Suppression in the Subgroup of IMA Patients with Right and Left IFGpo Damage

			p	
		Spearman's Rho	*Uncorrected*	*pFDR < .05*
LHD (n = 5)				
Central sites	Affected H	−0.5	.391	.854
	Unaffected H	0.2	.747	.854
Frontal sites	Affected H	−0.1	.873	.873
	Unaffected H	0.2	.747	.854
Parietal sites	Affected H	−0.2	.747	.854
	Unaffected H	0.5	.391	.854
Occipital sites	Affected H	0.3	.624	.854
	Unaffected H	0.4	.505	.854
RHD (n = 7)				
Central sites	Affected H	−0.955	**.001**	**.004**
	Unaffected H	−0.811	**.027**	**.043**
Frontal sites	Affected H	−0.775	**.041**	.055
	Unaffected H	−0.739	.058	.058
Parietal sites	Affected H	−0.811	**.027**	**.043**
	Unaffected H	−0.811	**.027**	**.043**
Occipital sites	Affected H	−0.739	.058	.058
	Unaffected H	−0.955	**.001**	**.004**

Significance represented in **bold**.

depicting each patient's lesion on a Damasio and Damasio (1989) set of standard templates (only lesion-containing slices are shown) is presented in Figure 2 (left IFGpo group, patients: AH, SCV, IO, BS, SB, IB, and DE; right IFGpo group, patients: FAM, UBC, YS, YM, SAK, YL, and AM).

Correlation between Mu Suppression and Apraxia Score in the Subgroup of IMA Patients with IFGpo Damage

Table 4 presents the Spearman's rho correlation coefficients between the magnitude of suppression at the lower mu range (8–10 Hz), as recorded in central sites (C3, C4), frontal sites (F3, F4), parietal sites (P3, P4), and occipital sites (O1, O2), and De Renzi's apraxia test scores in IMA patients with left IFGpo and right IFGpo damage (calculated separately for the affected and unaffected hemispheres). As can be seen in Table 4, De Renzi's apraxia test scores correlated significantly with the magnitude of mu suppression, both in the affected and unaffected hemispheres, at central and parietal sites, only in the RHD group. The magnitude of suppression in the 8–10 Hz in the unaffected hemisphere at occipital sites correlated significantly with De Renzi's apraxia test scores as well.

DISCUSSION

Traditionally, IMA is conceived as the outcome of failure to convert visual representations of movements into corresponding executable motor programs (Goldenberg, 2009, 2014). Our aim in the current study was to explore whether such conversion failure, as expressed in IMA patients' inability to imitate movements, is likely to result from damage to frontoparietal neurons with mirror properties. The rationale for the study has its basis in research findings pointing to a crucial role of the frontoparietal MNS in movement imitation and imitation-based learning in healthy individuals (Celnik et al., 2006, 2008; Stefan et al., 2005, 2008; Iacoboni, 2005; Buccino, Vogt, et al., 2004; Rizzolatti & Craighero, 2004; Iacoboni et al., 1999). These findings and related animal and human research led to motor control theorizing where the MNS is assumed to function as a means for direct coupling of afferent and efferent representations of biological movement (Rizzolatti & Kalaska, 2013; Rizzolatti & Sinigaglia,

2010). The involvement of disrupted MNS mechanisms in apraxia is in accord with studies that showed association between impaired action perception and action execution in apractic patients. For example, Buxbaum et al. (2005) found in LHD IMA patients a strong relationship between the capacity for object-related pantomime imitation and pantomime recognition. In another study, recognition of correct execution of familiar gestures performed by others was more impaired in patients with limb apraxia than in nonapractic patients (Pazzaglia et al., 2008).

To examine the role of the hMNS in apraxic imitation failure, we assessed first the magnitude of MNS activation, as signaled nonspecifically by mu suppression during observation of manual movement, in stroke patients who were classified as having IMA (on the basis of DeRenzi's clinical apraxia test), and then compared it with the magnitude of mu suppression shown in the same conditions by stroke patients without IMA. Suppression of the lower mu range during manual movement observation showed no significant difference between the two groups, following either LHD or RHD. Severity of imitation failure shown by IMA patients also did not correlate with the magnitude of MNS activation during action observation. These findings point to the involvement of mechanisms other than MNS dysfunction, at least in part of our sample of IMA patients.

As can be seen in Table 1, in these tests, several patients who scored below the cutoff for normality in De Renzi's test (i.e., those that belonged to the IMA group) had no visible damage to either IFG or IPL regions. It should be noted that, although apraxia is most frequently encountered following parietal and frontal damage, it was reported also following damage restricted to other brain areas, for example, temporal and subcortical regions (Petreska et al., 2007). Accordingly, our lesion analyses (Figure 2; Table 1) revealed in 4 of 11 RHD IMA patients and 6 of 14 LHD IMA patients, damage sparing both the opercular part of the IFG and the IPL (i.e., the cortical regions containing the major parts of the human MNS). In the majority of these patients, the lesion involved subcortical structures, and in one patient (AN of the RHD IMA group), the lesion was confined to midline structures supplied by the anterior-cerebral artery. The substantial number of IMA patients who had no damage to the cortical regions that contain the MNS may explain the lack of significant difference in the magnitude of mu suppression between patients with and without IMA. It can also explain the poor correlation between the magnitude of mu suppression and the apraxia test score.

The next analyses were restricted to subgroups of IMA patients—those with lesions involving either the aIPL or the IFGpo—that is, the cortical regions where the human MNS is assumed to reside (Fabbri-Destro & Rizzolatti, 2008; Morin & Grezes, 2008; Buccino, Lui, et al., 2004; Buccino, Vogt, et al., 2004), which are also areas most often affected in IMA patients (Goldenberg, 2009, 2014; Buxbaum et al., 2005; Weiss et al., 2001; Haaland et al., 2000). Among the 14 LHD patients with IMA, three had damage involving the IPL, three had damage involving the IFGpo, and two had damage involving both areas (overall, MNS areas were involved in 8 of the 14 LHD patients who exhibited imitation failure in DeRenzi's apraxia test). Among the 11 RHD patients with IMA, four had damage involving the IPL and three had damage involving the IFGpo (overall, MNS areas were involved in 7 of the 11 RHD patients who exhibited imitation failure in the apraxia test).

In our sample, all the five LHD patients and four of five RHD patients, in whom the lesion involved the IPL, had IMA. Our VLSM results corroborate the involvement of the left IPL in IMA formation. Five of seven LHD patients and all the seven RHD patients, in whom the lesion involved the IFGpo, had IMA. Thus, damage involving these two MNS regions resulted in apraxia in the great majority of cases. In the subgroup of RHD patients only, the role of MNS malfunction in the pathogenesis of apraxia was evidenced by a significant negative correlation between the severity of imitation failure exhibited in DeRenzi's apraxia test and the magnitude of mu suppression. In right IPL-damaged IMA patients, mu suppression recorded from the damaged hemisphere at central and frontal sites correlated significantly with De Renzi test's score (Table 3). Among IMA patients with involvement of the right IFGpo, the correlation between the severity of imitation failure and the magnitude of mu suppression recorded from damaged and undamaged hemispheres at central and parietal sites also reached significance (Table 4). Our lesion data are in partial agreement with findings obtained in functional imaging studies showing IPL activations during action observation, execution, and imitation (Caspers et al., 2010; Gazzola et al., 2007; Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006). Yet, Gazzola and Keysers (2009) found that activation during both action observation and execution is shared by more voxels in left compared with right parietal areas.

One point of interest emerging from the current study is the significant involvement of the right hemisphere in IMA. Although most studies on apraxia report a left hemisphere dominance for praxis, numerous studies suggest also involvement of the right hemisphere (Schell et al., 2014; Stamenova et al., 2010, 2012; Petreska et al., 2007; Heath et al., 2001; Roy et al., 2000; Marchetti & Della Sala, 1997; Haaland & Flaherty, 1984). Heath et al. (2001) analyzed pantomime and imitation performance of intransitive gestures (like the gestures used to assess the severity of apraxia in the current study) in a large sample of LHD and RHD stroke patients and found an equal prevalence and severity of apraxia in the two groups. Roy et al. (2000) found a similar prevalence and severity of apraxia in LHD and RHD stroke groups, as evidenced in imitation of transitive (object-related) gestures. Recently, Stamenova and colleagues (2010) found that RHD patients are more prone to err in imitation of

transitive gestures and LHD patients in imitation of intransitive gestures. In the current study, apraxia was diagnosed on the basis of failed imitation of intransitive, symbolic and nonsymbolic gestures (De Renzi et al., 1980). The rate of IMA was found to be quite similar in the two hemisphere groups—66.6% (14 of 21) and 73.3% (11 of 15) in the LHD and RHD groups, respectively. The average score in DeRenzi's apraxia test was also similar: 61.0 ± 9.2 and 59.8 ± 10.3 in LHD and RHD groups, respectively.

Imitation failure was associated clearly with MNS malfunction only among subgroups of RHD IMA patients. This finding was possibly an outcome of the fact that mu suppression values were obtained here during action observation sessions where movement learning for subsequent imitation was not part of the task definition (see Methods). Suchan, Melde, Herzog, Homberg, and Seitz (2007) showed using PET imaging that action observation done with the instruction to imitate the viewed movement activated the left parietal and premotor cortical areas, whereas action observation done with the instruction to judge movement velocity in the showed actions activates the two hemispheres. In the current study, patients were only asked to count silently the number of wide hand grasp and narrow grip movements shown in the videoclips. The fact that they were not required to learn the observed movement for the purpose of subsequent imitation may have contributed to the lack of an LHD effect on the correlation between apraxia test scores and mu suppression in the lower 8–10 Hz EEG range.

Furthermore, there is evidence suggesting that LHD affects more the control of movement trajectory, whereas RHD affects more the capacity to stabilize the limb in its target location at the end of the movement (Mani et al., 2013; Schaefer, Haaland, & Sainburg, 2007, 2009). Given that action observation and execution share a common mechanism implemented by the MNS, it is possible that our instructions to focus on the features of the final position (by counting the number of times where wide grasp and narrow grip movements occurred) engaged primarily the MNS on the right hemisphere, thus making the correlation between mu suppression and apraxia test scores more evident in the RHD IMA patients. In a recent study conducted by us in healthy participants, using a similar action observation paradigm, the overall magnitude of mu suppression during action observation was greater in the right hemisphere (Frenkel-Toledo et al., 2013; see also Perry & Bentin, 2009). We used the same action observation paradigm on stroke patients (Frenkel-Toledo et al., 2014). In that study, the magnitude of mu suppression showed a significant negative correlation with the extent of tissue damage in the right IPL but not in the homologous region of the left hemisphere. A very recent fMRI study aimed to identify precisely the human homologue of the frontal component of the MNS in the monkey (area F5c) disclosed a cortical region in the inferior part of the precentral sulcus, showing more intensive activation on the right hemisphere, with a specific sensitivity to the observation of the final stage of object-related manual movements (Ferri et al., 2015). Altogether, these findings strengthen the possibility that the specific characteristics of the task used in our recent and current action observation studies cause a recruitment of mirror neurons on the right than on the left hemisphere. It should be noted, though, that among the subgroup of patients with right IFGpo damage, the magnitude of mu suppression at the more anterior (central and parietal) sites correlated significantly with De Renzi's apraxia test scores, both in the affected (right) and unaffected (left) hemispheres. A possible explanation for the bihemispheral correlations could be the involvement of brain plasticity processes harnessing the unaffected hemisphere.

The lack of significant correlation between apraxia test scores and the magnitude of mu suppression in IMA patients with left IFGpo damage may stem also from greater susceptibility of left IFG neurons to top–down modulation (Chong, Cunnington, Williams, & Mattingley, 2009; Chong, Williams, Cunnington, & Mattingley, 2008). Chong et al. (2008) found that task demands modulate the level of left IFG activation during action observation suggesting a key role for this region in gating the perceptual input to the MNS, thus limiting perceptual processing of movements that are task-irrelevant. In keeping with this interpretation, Chong et al. (2009) showed that attention modulates the tendency for imitation of observed movements in a manner that enables the observation–execution matching processes to be flexible and adaptive, in accord with the requirements of the ongoing task. Indeed, humans are confronted with a myriad of gestures in daily life. However, they do not imitate automatically those that are not behaviorally relevant to them. As said, task requirements in our study were to count silently the number of times specific gestures occurred on the screen and to avoid moving during the video clip observation. Thus, task demands probably dictated a state of reduced MNS recruitment manifested by down-regulation of mu suppression. According to Chong et al. (2008, 2009), this effect is likely to be more pronounced in the mirror neurons of the left IFGpo region, a fact that could contribute to the lack of correlation between apraxia test scores and the magnitude of mu suppression in IMA patients with left IFGpo damage, in contrast to the significant correlation found in IMA patients with right IFGpo damage.

De Renzi's aparaxia test scores correlated significantly also with the magnitude of posterior alpha suppression in the unaffected hemisphere in both the subgroup of IMA patients with right IPL damage and in the subgroup of IMA patients with right IFGpo damage. The alpha range suppression recorded from occipital electrodes might reflect the recruitment of visual attention and working memory in the movement observation task (Perry et al., 2011; Klimesch et al., 2007; Klimesch, 1997; Khulman, 1978),

which in the current study required attentive silent counting of the number of times specific gestures occurred on the screen during video clip observation. Thus, the correlation between posterior alpha suppression and imitation capacity is likely to suggest a multifactorial mechanism for IMA, with a possible impact for deranged visual attention (signaled by posterior alpha suppression) beyond the effect of MNS damage (signaled by central mu suppression).

Conclusions

The conclusions emerging from the current study can be summarized as follows:

a. Damage to various cortical and subcortical structures in both hemispheres can result in imitation deficits typical of IMA (this finding corroborates earlier reports by Petreska et al., 2007).
b. Neither direct structural damage to cortical regions where the MNS reside nor evidence of physiological malfunction of this system (at least as evidenced in the magnitude of mu suppression) is a prerequisite for IMA formation.
c. The great majority of stroke patients with damage involving the IPL and/or the IFGpo, that is, the areas of the ventral frontoparietal cortex that contain the major parts of the human MNS, manifest impaired movement imitation typical of IMA.
d. Among these patient subgroups, a significant negative correlation between the severity of imitation failure and the magnitude of mu suppression shown during action observation was found only in patients with RHD. This finding points to a role for right MNS malfunction in IMA formation.

Several caveats of the current study need to be taken into consideration. First, following our recent action observation studies (Frenkel-Toledo et al., 2013, 2014) we set task requirements for the action observation sessions that could lead to preferential recruitment of the MNS on the right hemisphere (as explained before). Second, the negative correlation between apraxia severity and the magnitude of mu suppression was found here in IMA patients with lesions involving cortical regions that contain large aggregates of mirror neurons (i.e., the IPL and IFGpo; see Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014, for a recent review). This fact raises the possibility that the correlation reflects sharing of a common synaptic space by praxis and mirror mechanisms, without demonstration of a causative role for the latter in the formation of IMA. Given the fact that the correlation reached statistical significance, such interpretation is unlikely, but cannot be completely dismissed. Demonstration of double dissociation rather than association patterns could be more informative. Third, our attempt to investigate further the link between mu suppression and apractic imitation failure by conducting VLSM analyses (Bates et al., 2003) for mu suppression indices obtained from each hemisphere and the apraxia test scores, separately for the LHD and RHD groups, showed that the basic VLSM requirement of having at least three participants with damage to a specific voxel (Haramati et al., 2008) was not fulfilled within our sample for much of the voxel data in the ROIs (see Methods and Results). Therefore, identification of one cluster of cortical voxels associated with reduced imitation capacity (involving the IPL, superior parietal lobule, and post central gyrus) only in the LHD patients group requires further investigation using a larger sample. Such investigation together with a conjunction VLSM analysis (Buxbaum et al., 2014; Bates et al., 2003) would clarify if there are particular brain regions that affect both imitation capacity (De Renzi's apraxia test scores) and mu suppression.

It should be noted that the clinical test of apraxia used here (De Renzi et al., 1980) consists of intransitive gestures whereas the mu suppression values were obtained during observation of transitive movements. This difference in gesture types could affect the correlation.

In future work, it would be of interest to test the correlation between apraxia severity and the magnitude of mu suppression obtained during action observation done in the context of motor learning, that is, for the purpose of learning the viewed motor actions. In that context, praxis errors of different types (e.g., in imitation of transitive and nontransitive, symbolic and nonsymbolic gestures) can be correlated with the magnitude of mu suppression revealed during observation of similar gestures versus gestures of a different type. Given the specificity of movement types encoded by different populations of mirror neurons (Rizzolatti et al., 2014), this approach is likely to examine the question of MNS contribution to praxis in a more precise manner by enabling dissociation patterns to occur, thus corroborating the interpretation of our correlation findings. With larger numbers of examined patients, such an approach may shed light on the contribution of MNS dysfunction to the emergence of different types of praxis errors that were found to have distinctive lesion patterns (e.g., postural setting in tool use vs. the kinematics of meaningless intransitive movement; Buxbaum et al., 2014; Hoeren et al., 2014).

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