

COGNITIVE NEUROSCIENCE

Modulation of cortical motor outputs by the symbolic meaning of visual stimuli

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Abstract

The observation of an action modulates motor cortical outputs in specific ways, in part through mediation of the mirror neuron system. Sometimes we infer a meaning to an observed action based on integration of the actual percept with memories. Here, we conducted a series of experiments in healthy adults to investigate whether such inferred meanings can also modulate motor cortical outputs in specific ways. We show that brief observation of a neutral stimulus mimicking a hand does not significantly modulate motor cortical excitability (Study 1) although, after prolonged exposure, it can lead to a relatively nonspecific modulation (Study 2). However, when such a neutral stimulus is preceded by exposure to a hand stimulus, the latter appears to serve as a prime, perhaps enabling meaning to the neutral stimulus, which then modulates motor cortical excitability in accordance with mirror neuron-driving properties (Studies 2 and 3). Overall results suggest that a symbolic value ascribed to an otherwise neutral stimulus can modulate motor cortical outputs, revealing the influence of top-down inputs on the mirror neuron system. These findings indicate a novel aspect of the human mirror neuron system: an otherwise neutral stimulus can acquire specific mirror neuron-driving properties in the absence of a direct association between motor practice and perception. This significant malleability in the way that the mirror neuron system can code otherwise meaningless (i.e. arbitrarily associated) stimuli may contribute to coding communicative signals such as language. This may represent a mirror neuron system feature that is unique to humans.

Introduction

Excitability in the primary motor cortex can be modulated by mere observation of a motor action (Fadiga *et al.*, 1995). Such facilitation is highly specific for muscles involved in the observed action, depends on the observer's point of view and is presumed to be mediated by the activation of the mirror neuron system (Rizzolatti & Craighero, 2004; Fadiga *et al.*, 2005). The mirror neuron system appears to have the property of extracting the meaning of an action beyond the specific visual features perceived. For example, mirror neurons in the macaque brain can be activated even when the observed action does not strictly correspond to its motor representation, such as when the visual description of a given action is incomplete (Umiltà *et al.*, 2001). Observation of hand shadows also appears to activate the hand motor resonance system (Fadiga *et al.*, 2006). Moreover, mirror neurons have been shown to respond to the observation of tool actions after prolonged exposure, suggesting generalization of the response

whereby the tool is viewed as a prolongation of the hand (Ferrari *et al.*, 2005). In humans, actions performed by a robot can also activate the human mirror neuron system to a similar extent as the equivalent human action (Press *et al.*, 2005; Gazzola *et al.*, 2007).

In all of these cases, modulation of the mirror system is induced by actions or objects with an obvious and explicit link to the actual movement. In a functional magnetic resonance imaging study (Reithler *et al.*, 2007), the visual and motor descriptions of an action sequence were dissociated by having participants practice specific movement sequences (tracing maze trajectories) without visual input. Volunteers were subsequently scanned while a visual rendering of the practiced path, or that of an unpracticed path, was presented. It was found that visual presentation of the previously practiced, but unseen, motor sequence activated mirror neuron areas such as the ventral premotor cortex and the inferior parietal lobule, suggesting that a novel visual stimulus can elicit motor activity by way of nonvisual motor learning. Thus, it seems that strong visuomotor associations can be elicited if an observed action, or its abstract representation, is part of the observer's motor repertoire (Calvo-Merino *et al.*, 2006; Cross *et al.*, 2006).

In the present study we aimed to extend such observations by examining whether an initially neutral visual stimulus might eventu-

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ally become symbolically linked to a body-part motor action and thus be sufficient to elicit mirror neuron activity in the absence of motor practice. Four experiments applying single-pulse transcranial magnetic stimulation (TMS) over the left primary motor cortex and recording motor-evoked potentials (MEPs) from the right hand were designed to answer two specific questions:

(1) Does observation of images representing arrays of dots mimicking a hand (i.e. an otherwise neutral visual representation) elicit corticospinal excitability changes in the primary motor cortex?

(2) Does observation of images representing arrays of dots mimicking a hand (i.e. an otherwise neutral visual representation) modulate corticospinal excitability differently when primed with images of hands (i.e. concrete representation)?

Materials and methods

Experimental subjects

A total of 52 healthy volunteers took part in the experiment (27 women, mean age 26 years, range 19–40 years): 16 in Study 1 (Hands and Dots stimuli), 16 in Study 2 ($n = 8$ in the Hands Condition, $n = 8$ in the Dots Condition), 16 in Study 3 ($n = 8$ in the Hands–Dots Condition, $n = 8$ in the Dots–Dots Condition) and 16 in Study 4. All participants were right-handed as tested using the Edinburgh Handedness Inventory. All participants gave written informed consent prior to entering the experiment, which was approved by Beth Israel Deaconess Medical Center's Institutional Review Board.

Experimental tasks

The first three studies employed TMS. Participants were instructed to observe sequences of hand pictures (with either the index or the five fingers outstretched) or sequences of arrays of five dots (with either one filled and four empty dots or five filled dots) (Fig. 1A). When sequences of hands were displayed, participants were asked to silently count how many times one finger instead of five was outstretched. When sequences of dots were displayed, participants had to silently count how many times one instead of five dots was filled. Participants were also presented with sequences of a single dot (baseline condition) and asked to count how many dots were filled. Participants had to report their response at the end of each sequence. They were told that the aim of the study was to evaluate 'the effects of counting on the brain'. Each experimental sequence included 10 stimuli mimicking only the right or only the left hand. Stimuli were pseudo-randomly

presented. For each sequence of stimuli, a single TMS pulse was applied over the left primary motor cortex to evoke MEPs in the muscle relevant to the study (see details below). The TMS pulse was pseudo-randomly triggered after presentation of at least seven stimuli (Fig. 1B). The interstimulus interval between TMS pulses was at least 10 s to minimize possible carry-over effects. Visual stimuli and TMS pulses were triggered using Presentation software (Neurobehavioral Systems, Inc., <http://www.neurobs.com>). Stimuli were presented on a 17" high-resolution PC computer screen set at eye level at a distance of 1 m.

Transcranial magnetic stimulation and motor-evoked potential recording

Participants sat comfortably during the entire experiment. TMS pulses were delivered over the primary motor cortex of the left hemisphere, with a commercially available 80-mm figure-of-eight coil and a SuperRapid Magnetic Stimulator (Magstim Co., UK). The current waveform was biphasic and the orientation of the stimulation coil was 45° from the midline with the handle pointing backwards. The stimulation intensity was set at 120% of the individual's resting motor threshold (mean $34.2 \pm 7.8\%$), except for two subjects (Study 1), where an intensity of 130% motor threshold was used to obtain a reliable baseline response. The motor threshold and optimal scalp site to induce MEPs were defined as the minimum TMS intensity required to induce MEPs of $> 50 \mu\text{V}$ peak-to-peak amplitude in at least five of 10 trials in the contralateral first dorsal interosseus (FDI) muscle (Studies 1 and 2) and in both the contralateral FDI and abductor digiti minimi (ADM) muscles (Study 3). The coil position was marked over a Lycra swimming cap for each participant in order to minimize variability in the targeted brain area. Relaxation of the target muscle(s) was documented by electromyographic recording for at least 40 ms before each TMS pulse. MEPs were recorded using pairs of Ag/AgCl surface electrodes placed over the FDI (Studies 1 and 2) and both the FDI and ADM (Study 3) of the right hand. A circular ground electrode was placed on the participant's wrist. The electromyographic signal was recorded using a PowerLab 4/30 system (ADInstruments, Colorado Springs, USA), filtered with a band pass of 20–1000 Hz and digitized at a sampling rate of 4 kHz. Data were stored on a Macintosh MacBook Pro computer (Apple Computers, Cupertino, CA, USA) for offline analysis. The area under the curve of the collected MEPs was measured using SCOPE software (ADInstruments), averaged for each stimulus type and expressed as a percentage of the baseline mean (MEPs recorded when viewing sequences of single dots). Ten MEPs at rest were recorded before and at the end of the stimuli presentation.

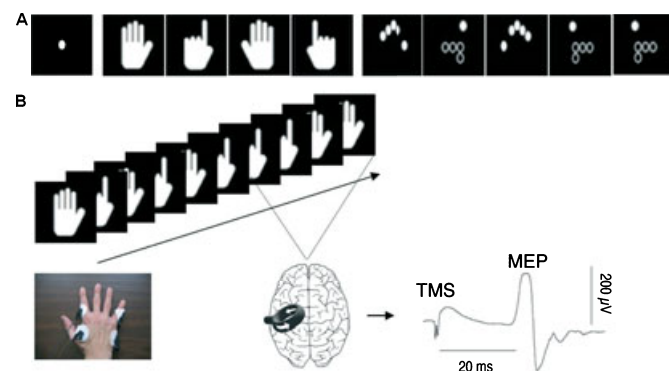


FIG. 1. Study design. (A) Stimuli were nine pictures of a single dot and of arrays of dots and hands, which could mimic/represent either the right or left hand. (B) Schematic representation of the stimuli and TMS.

Results

The goal of Experiment 1 was to evaluate the modulation of MEP amplitude during observation of either the hand or the dot stimuli. A first group of participants observed 30 sequences of the right and left hand stimuli and 30 sequences of single dots. A second group observed 30 sequences of dots mimicking the right and left hand and 30 sequences of single dots. It was expected that the hand stimuli would elicit greater cortical excitability change as compared with the dots. In order to test this, we submitted the change in MEP amplitude (in percent from baseline) to a 2×2 mixed ANOVA [2 Conditions (Hands, Dots: between) \times 2 Orientations (Right, Left: repeated)]. There was no main effect ($P > 0.05$). However, there was a significant interaction between Condition and Orientation ($F_{1,14} = 4.47$,

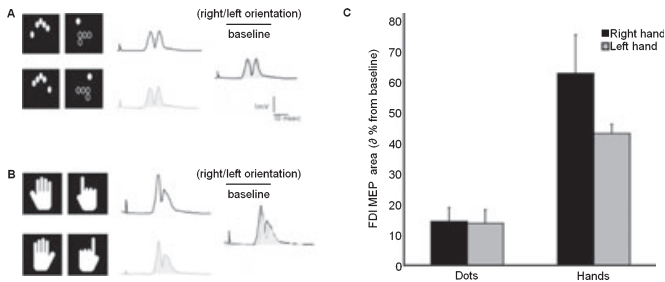


FIG. 2. Examples of rectified TMS-induced MEP when participants were observing (A) the dot stimuli mimicking the right and left hand, and (B) the right and left hand stimuli. (C) The graph illustrates the ratio of MEP size of both the right and left orientations on baseline.

$P < 0.05$; $\eta^2 = 0.24$; Fig. 2). A series of planned Bonferroni comparisons revealed that, for the Hands Condition, observation of the right hand induced a significantly greater MEP change ($M = 61\%$, $SD 41.60$) than that of the left hand [$M = 42\%$, $SD 32.84$; $t_7 = 3.22$, $P < 0.02$; $\eta^2 = 0.60$]. For the Dots Condition, there was no significant difference in MEP change between the dots mimicking the right and the left hand [$t_7 = 0.10$, $P > 0.05$]. Findings from this first experiment showed that observation of a known stimulus (Hands Condition) significantly modulated motor cortical excitability in accordance with the mirror neuron system (i.e. respecting the laterality of the hand presented and revealing differences for right vs. left hand stimuli). However, observation of a neutral stimulus mimicking a hand (Dots Condition) did not significantly modulate motor cortical excitability.

The goal of Experiment 2 was to test whether exposure to the hand stimuli could prime the brain to see hands when subjects observed the dots. Specifically, we tested whether a stimulus known to modulate motor excitability in the primary motor cortex according to the predictions of the mirror system (i.e. Hands Condition as shown in Experiment 1) would prime motor excitability such that an otherwise neutral stimulus would then modulate cortical excitability in accordance with mirror properties (i.e. Dots Condition as shown in Experiment 1). Unlike Experiment 1, participants in Experiment 2 had to observe two blocks of stimuli and one block of single dots, and TMS-induced MEPs were collected during presentation of the second block of stimuli (Fig. 3). Each stimulus type was presented for a total of 30 sequences. One group of participants first observed a block of hand stimuli then a block of dot stimuli (Hands–Dots Condition; stimuli representing the right or left hands). A second group of

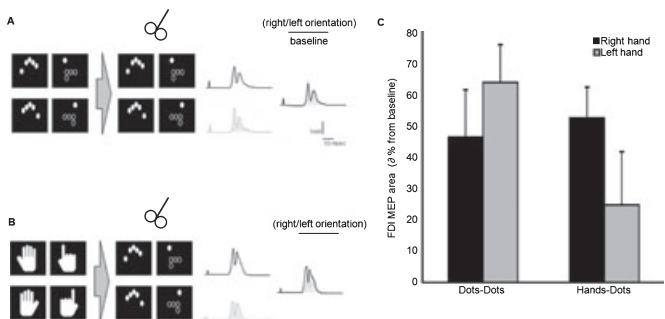


FIG. 3. Examples of rectified TMS-induced MEP when participants were observing the dot stimuli mimicking the right and left hand after observing (A) a block of dot stimuli or (B) a block of hand stimuli. (C) The graph shows the ratio of MEP size of both the right and left orientations on baseline.

participants observed two blocks of dot stimuli (Dots–Dots Condition). This group provided a control to test whether prolonged observation of the dot stimuli would lead to perception of meaningful stimuli such as hands or to modulation of cortical motor outputs. Data were submitted to a 2×2 mixed ANOVA [2 Conditions (Hands–Dots, Dots–Dots: between) \times 2 Orientations (Right, Left: repeated)] to test whether cortical excitability during observation of dots was different when preceded by observation of hand stimuli or by observation of more dot stimuli. There was no main effect ($P > 0.05$). However, there was a significant interaction between Condition and Orientation ($F_{1,6} = 13.14$, $P < 0.05$; $\eta^2 = 0.56$; Fig. 3). Bonferroni comparisons revealed that, for the Hands–Dots Condition, there was a significant difference in MEP change between the Right and Left Orientation [$t_7 = 4.24$, $P < 0.02$; $\eta^2 = 0.86$; Right Orientation: $M = 53\%$, $SD 9.90$ $>$ Left Orientation: $M = 24\%$, $SD 16.89$]. For the Dots–Dots Condition, the difference in MEP change between the Right and Left Orientation did not reach statistical significance [$t_7 = -1.65$, $P > 0.05$]. These data indicate that a priming stimulus can modulate motor excitability and modify the processing of a previously neutral stimulus in accordance with mirror neuron-driving properties (Hands–Dots Condition). In addition, we found that prolonged observation of a neutral stimulus ultimately enhances excitability in the primary motor cortex but in a relatively nonspecific way (Dots–Dots Condition).

The goal of Experiment 3 was to test whether the priming effect found in Experiment 2 was specific to the muscle involved in the observed action. In other words, does the observation of dots, after that of hands (in which the index or the five fingers are outstretched), modulate cortical excitability only for the relevant muscle or are the neighboring muscles also involved? MEPs were recorded from the FDI and ADM muscles during observation of the same stimuli as presented in Experiment 2 (Hands–Dots Condition with the right or left hands; 30 sequences for each stimuli type and one block of single dots) and TMS was applied during the dot stimuli. Data were submitted to a 2×2 repeated-measures ANOVA [2 Orientation (Right, Left) \times 2 Muscle (FDI, ADM)] in order to examine the specificity of the modulation of motor cortical outputs by the dot stimuli primed by preceding hand stimuli. Results revealed no main effect ($P > 0.05$) but the interaction between Orientation and Muscle was close to significance ($F_{1,3} = 8.50$, $P = 0.06$; $\eta^2 = 0.74$). These findings show that the priming effect was greater for the FDI, the muscle involved in the observed action, as compared with the ADM (Fig. 4). These findings suggest that the modulation of the primed stimulus is indeed specific; enhancement of cortical excitability for the FDI followed the constraints expected for the mirror neuron system, whereas this was not the case for the ADM, which was not involved in the task.

In Experiment 4, we assessed the subjective perception of hand and dot stimuli. Two groups of participants were presented with the same visual stimuli and instructions used in Experiment 2 (Hands–Dots

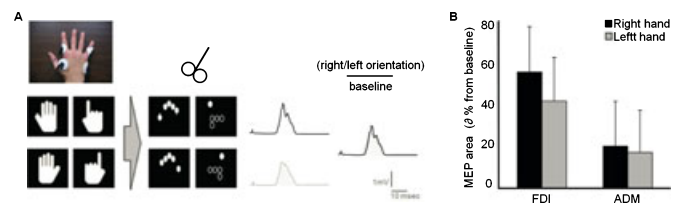


FIG. 4. (A) Examples of rectified TMS-induced MEP when participants were observing the dot stimuli mimicking the right and left hand after observing a block of hand stimuli. (B) The graph illustrates that the ratio of MEP size of the difference between the dot stimuli mimicking the right and left hand on baseline was greater for the FDI- than the ADM-related cortical excitability.

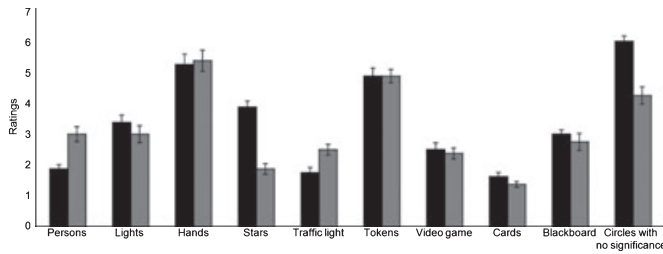


FIG. 5. Rating on a scale (1, not at all; 7, very much) of the degree to which each of the following elements were represented by stimuli. Columns in black and gray represent the Dots–Dots Condition and Hands–Dots Condition, respectively. The stimulus category is on the X-axis and the judgment score on the Y-axis.

Condition and Dots–Dots Condition) and asked to complete a three-part questionnaire afterwards. The questionnaire included two open questions: (i) ‘What did you see?’ and (ii) ‘What did the dot stimuli represent?’. Furthermore, participants were asked to rate on a scale ranging from 1 to 7 the degree to which each of the following elements were represented by the arrays of dots: 1, persons; 2, lights; 3, hands; 4, stars; 5, traffic light; 6, tokens; 7, video game; 8, cards; 9, blackboard; and 10, circles with no significance. On the first question (What did you see?), all 16 participants responded either ‘dots’ or ‘circles’. On the second question (What did the dot stimuli represent?), six out of eight participants in both groups (Hands–Dots; Dots–Dots) guessed ‘fingers’ or ‘hands’. Ratings from the third question on the representation of the dots and hands were submitted to a mixed 2×10 ANOVA with Group (Dots–Dots, Hands–Dots) as the between-subjects factor and Representation (the 10 elements) as the within-subjects factor. There was a main effect of Representation ($F = 10.10$; $P < 0.001$) and no main effect of Group ($F = 0.510$; $P > 0.05$). There was also no significant interaction between factors ($F = 1.30$; $P > 0.05$). Ratings are illustrated in Fig. 5. These findings show that most subjects reported that the dots represented fingers or hands when they were explicitly asked.

Discussion

The mirror neuron system provides a neural substrate for modulation of motor outputs on the basis of the observation of an action and the modulation is specific to the motor cortical outputs engaged in the observed action. As humans, we respond to visual percepts not only by their immediate meaning but also given their symbolic significance. Our study demonstrates that motor cortical outputs are modulated by the symbolic value of an otherwise neutral visual stimulus with prolonged observation and this modulation can be refined when primed with a more concrete visual stimulus. Specifically, we found that observation of an otherwise neutral stimulus mimicking a hand did not significantly enhance motor cortical output excitability, supporting and extending previous research showing that cortical excitability is not modulated by passively viewing a moving dot (Gazzola *et al.*, 2007). However, when observation of this neutral stimulus was prolonged, and the dots were presented in a very specific arrangement, there was a significant facilitation of motor cortical outputs. This modulation was, however, somewhat nonspecific (i.e. occurred regardless of whether the stimuli were representing the right or left hand). However, when hand stimuli were used as primes, the neutral stimuli elicited a specific facilitation (relative to the hand laterality), presumably suggesting that the prime endowed the dot stimuli with greater and more specific symbolic significance. Our

results support the findings of Stanley *et al.* (2007) who found that a congruency effect of dot motion was observed in subjects who were told that the movement was performed by a human but not in those who were told that the movement was computer generated, suggesting that a dot in itself does not elicit a specific response but can become meaningful depending on what the subjects believe the dot motion represents.

The mirror neuron activity may be preferentially elicited by biological, natural movement (Kilner *et al.*, 2004; Tai *et al.*, 2004; Press *et al.*, 2005; Gazzola *et al.*, 2007; Reithler *et al.*, 2007). Here we report that cartoon stimuli conveying minimal information on the underlying movement can also trigger the corresponding motor representations and respond to the same mirror neuron properties: (i) observation of cartoon hands in movement increased corticospinal excitability and this increase was (ii) greater for the contralateral hand (e.g. Aziz-Zadeh *et al.*, 2002) and (iii) muscle specific (Fadiga *et al.*, 1995; Maeda *et al.*, 2002).

The main novel finding of this work is that stimuli that do not initially drive the mirror neuron system in a specific manner can acquire mirror properties through priming. In previous work, the mirror neuron system was activated by visual stimuli conveying action meaning to the observer, such as reading of action phrases (Aziz-Zadeh *et al.*, 2006) or observation of robotic movements (Gazzola *et al.*, 2007). Here, it appears that the priming stimulus conveyed symbolic value to another stimulus such that motor associations were transferred to this other stimulus. It has been suggested that mirror neuron system activity depends on experienced contingency and that stimulus response learning underlies mirror system responses. Our findings support such sensorimotor theories of action observation (e.g. Pineda, 2008; Catmur *et al.*, 2009). The initial presentation of dot stimuli did not modulate motor cortical output, presumably due to absent or minimal activation of mirror activity. However, following presentation of the prime, the same dot stimuli appeared to connect through visuomotor association with specific hand actions, supporting the notion that mirror properties arise through correlated visual experience. This suggests that the mirror neuron system can also be modulated without sensorimotor learning through mere visual perception of static cartoon stimuli. This also indicates that a symbolic value ascribed to an otherwise neutral stimulus can modulate motor cortical outputs revealing the influence of top-down inputs on the mirror neuron system. This is in line with the predictive coding model proposed by Kilner *et al.* (2007). They suggest that the mirror neuron system is predictive, instead of a simple feedforward recognition model with connections from low to high level representations of an action. In the framework of Kilner *et al.* (2007), the predictive coding of understanding an action is conveyed by both lower and higher level representations with reciprocal exchange of signals. Therefore, the intention of an action can be processed without sensory inputs. Our data seem to fit very well within their model.

It is also interesting to highlight that motor cortical outputs were modulated during a task when subjects had to simply count the number of specific events (single dots or finger movements). Furthermore, the modulation was specific for the hand (left or right) even though subjects remained unaware of the presence of lateralized (left or right) hand stimuli. It has also been suggested that the mental lexicon of actions supported by mirror neurons may be abstract and independent of concrete motoric features (Rizzolatti *et al.*, 1996; Galati *et al.*, 2008; Lestou *et al.*, 2008) and does not depend on visual features (Turella *et al.*, 2009). Here, participants were asked to count the dots representing the tip of the index finger. By doing so, it is possible that they may have imagined performing the movement of stretching their own index finger. Thus, counting

an otherwise abstract stimulus, when primed with the hand stimulus, may have induced appropriate motor imagery (Aziz-Zadeh & Ivry, 2009).

Some have proposed that motor practice is needed to associate a visual stimulus to motoric representations (Calvo-Merino *et al.*, 2006; Cross *et al.*, 2006; Reithler *et al.*, 2007). The present results suggest, however, that motor practice, at least of a simple common hand movement, is not required to activate motor representations. Although finger movements are part of the observer's motor repertoire, a direct coupling between the array of dots and motor activity was never explicitly constructed in the present study. This supports the idea that general principles of inference based on visual experience can be sufficient to activate mirror neurons but the complexity of movement might modulate the visuomotor association. It is of note here that the movement implied was simple and common (i.e. index stretching) as compared with those studied in previous work (i.e. dancing movements involving the whole body). Furthermore, nonvisual motor training can enhance visual perception capabilities (Casile & Giese, 2006; Reithler *et al.*, 2007). The present results support the idea that the opposite may also be true: nonmotor visual experience may enhance and refine neurophysiologic motor responses. This may carry clinical relevance, especially for patients with spinal cord injury and traumatic brain injury who have no or limited motor capacities but still have existing mirror neuron activity (Fecteau *et al.*, 2010). Visual training, such as observation of movements, seems to contribute to ameliorating motor functions in stroke patients (Celnik *et al.*, 2008). From a more general perspective, the present results are in line with the idea that behavioral experience can refine neurophysiologic responses and modulate brain plasticity (Pascual-Leone *et al.*, 2005).

It is not clear whether our participants were aware of the stimulus nature during the experiment. When we specifically asked participants to tell us what they saw, they simply responded 'dots'. However, when explicitly asked to guess what the dots might represent, most subjects in Experiment 4 guessed fingers or hands. However, we cannot say for sure that subjects in Experiments 2 and 3 saw hands in the dots. Regardless, both groups (those who saw an actual hand and those who did not) responded in the same way to the questionnaires, suggesting that whatever the degree to which they could recognize hands, it was not enough to give the dots a mirror neuron-driving value when a real hand was not previously seen in that context. These findings suggest that a stimulus can acquire mirror neuron properties regardless of motor practice. This seems to be true even if the stimulus is abstract (regardless of subjective awareness of the symbolic meaning).

In summary, we present here a novel feature of the human mirror neuron system that allows an otherwise neutral visual stimulus to acquire specific mirror neuron-driving properties in the absence of a direct association between motor practice and visual perception. These data suggest significant malleability in the way that the mirror neuron system codes observed actions and contributes to action understanding. This property of the mirror neuron system may be uniquely human and be acquired developmentally along with communication codes such as language. Comparative and longitudinal studies would provide valuable insights in this regard.

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Abbreviations

ADM, abductor digiti minimi; FDI, first dorsal interosseus; MEP, motor-evoked potential; TMS, transcranial magnetic stimulation.

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