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SHORT COMMUNICATION
Left hemisphere motor facilitation in response to manual action sounds

Lisa Aziz-Zadeh,[1,2] Marco Iacoboni,[1,3,4] Eran Zaidel,[2,4] Stephen Wilson[1,5] and John Mazziotta[1,3,4,6]

[1]Ahmanson Lovelace Brain Mapping Center, Neuropsychiatric Institute, UCLA, 660 Charles E. Young Dr. South, Los Angeles, CA90095–7085, USA

[2]Departmentof Psychology, University of California at Los Angeles, Los Angeles, CA 90095, USA

[3]Department of Psychiatry and Biobehavioural Sciences, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095, USA

[4]Brain Research Institute, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095, USA

[5]Neuroscience Interdepartmental Program at UCLA, Los Angeles, CA, USA

[6]Departments of Neurology, Pharmacology and Radiological Sciences at UCLA, Los Angeles, CA, USA

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Abstract

Previous studies indicate that the motor areas of both hemispheres are active when observing actions. Here we explored how the motor areas of each hemisphere respond to the sounds associated with actions. We used transcranial magnetic stimulation (TMS) to measure motor corticospinal excitability of hand muscles while listening to sounds. Sounds associated with bimanual actions produced greater motor corticospinal excitability than sounds associated with leg movements or control sounds. This facilitation was exclusively lateralized to the left hemisphere, the dominant hemisphere for language. These results are consistent with the hypothesis that action coding may be a precursor of language.

Introduction

A major speech area in the human brain is Broca's area. This area is located in the left hemisphere, on the lateral wall of the most anterior part of the human brain, the frontal lobe. Some have suggested that the language properties of Broca's area evolved from a communication system based on 'mirror' neurons, premotor neurons that fire when monkeys perform goal-directed actions but also when monkeys observe somebody else making the same actions (Gallese *et al*., 1996; Rizzolatti & Arbib, 1998; Arbib, 2001). A mirror system for manual actions may have been important in establishing a means of nonverbal communication and, from this system, neural properties supporting language might have evolved (Hari *et al*., 1998; Fadiga *et al*., 2002; Meister *et al*., 2003). The critical role of Broca's area in manual imitation (Krams *et al*., 1998; Iacoboni *et al*., 1999; Koski *et al*., 2002; Grezes *et al*., 2003; Heiser *et al*., 2003; Koski *et al*., 2003) supports this hypothesis. Furthermore, the recent discovery of auditory mirror neurons, premotor neurons that fire when the monkey makes an action, watches the same action or hears the sound of the action (e.g. breaking a peanut) in the dark, has tied this system to the auditory modality, important for human speech (Kohler *et al*., 2002; Keysers *et al*., 2003).

Is the mirror system in fact a precursor of language? One way to better explore this question is to investigate the system's laterality in the human brain. Each cerebral hemisphere is known to have different specializations and serve different functions. Language is lateralized to the left hemisphere while spatial abilities are lateralized to the right hemisphere (Zaidel, 1978). Human premotor areas with mirror properties concerned with visually presented actions, however, have not shown a clear lateralization (Koski *et al*., 2002). A previous single-pulse transcranial magnetic stimulation (TMS) study similarly demonstrated corticospinal facilitation in both left and right motor cortices during action observation, an effect probably due to mirror properties in both hemispheres (Aziz-Zadeh *et al*., 2002b). A limited asymmetry observed in that study was probably due to asymmetric motor control in right-handers (Kim *et al*., 1993; Chen *et al*., 1997). Furthermore, an analysis of a large functional magnetic resonance imaging (fMRI) dataset comprising 58 subjects observing and imitating hand actions has shown bilateral activations in premotor areas with mirror properties (Molnar-Szakacs *et al*., 2002). Moreover, a recent study using repetitive TMS, a technique that induces transient disruption of function in stimulated brain areas, has shown imitative deficits when either Broca's area or its homologue in the right hemisphere were stimulated (Heiser *et al*., 2003). Thus, the evidence does not suggest left hemisphere lateralization for the human mirror system in the visual domain.

With regard to the human mirror system in the auditory domain, there is TMS evidence for left hemisphere sensitivity to speech sounds, such as phonemes (Fadiga *et al*., 2002; Watkins *et al*., 2003). However, hemispheric effects of action sounds not associated with speech have not been explored until now. If manual action sounds also show left

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Correspondence: Dr Lisa Aziz-Zadeh, as above.
E-mail: lazadeh@loni.ucla.edu

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hemisphere lateralization, this may suggest that action understanding through the auditory channel, in general, is a function lateralized to the left hemisphere, as speech seems to be. This would support the hypothesis of evolutionary continuity between the mirror system and the neural systems associated with language functions (Rizzolatti & Arbib, 1998).

We examined the sensitivity of human mirror areas to the auditory modality by using single-pulse TMS over the left and right hemisphere primary motor cortices. With this technique, one can measure motor excitability under different experimental conditions (Fadiga *et al*., 1995; Aziz-Zadeh *et al*., 2002b). A strong asymmetry in motor excitability may suggest hemispheric specialization. Twenty-four normal right-handed subjects listened to one of two kinds of bimanual hand action sounds (typing or tearing paper), to a bipedal leg action sound (walking), and to a control sound (thunder). We used bimanual action sounds to minimize hemispheric differences due to hand preference. As subjects listened to each sound, motor evoked potentials (MEPs) were recorded from the first dorsal interosseus (FDI) hand muscle contralateral to the hemisphere stimulated. If motor facilitation to action sounds occurs then one would expect that, when recording from the hand muscle, larger MEPs would be observed for hand action sounds than for leg action sounds. Furthermore, positing that the acoustic modality for manual action sounds is in fact a precursor to language processing, we predicted that this effect would be observed in the left hemisphere.

Materials and methods

Twenty-eight subjects were recruited for this study (13 males, 15 females; mean age 26, range 18–50 years). Four subjects (one male, three females) were excluded from the study due to the inability to measure consistent MEPs from one hemisphere. All subjects were right-handed according to a modified Oldfield Handedness Questionnaire (Oldfield, 1971). The subjects were screened using a questionnaire for neurological, psychiatric and medical problems, and contraindications to TMS (Wassermann, 1998). The UCLA Institutional Review Board approved the study and written informed consent was obtained from all subjects. Therefore, this study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki.

To record MEPs, we placed two 10-mm gold surface electrodes on the belly and tendon of each subject's right (and left) FDI muscle. A velcro ground electrode was placed on the right (and left) upper arm. All of these sites were appropriately cleansed with alcohol prior to electrode attachment.

Single pulses of TMS were delivered through a 90-mm angled figure-of-eight coil using a monophasic Cadwell High Speed Magnetic Stimulator to the right (and left) 'optimal scalp site'. This was defined as the scalp position and coil orientation where TMS-induced MEPs were maximal in the FDI muscle. MEPs were collected with the muscles at rest (amplification ×1000–5000, band pass filter 0.3–1000 Hz, digitization sampling rate of 2 kHz/channel). The motor threshold (MT) was defined as the minimal intensity that induced MEPs $>50\,\mu$V peak-to-peak amplitude in at least 5 out of 10 trials. Single-pulse TMS was delivered at 120% of the subjects' MT for all trials. Sixty MEPs were collected in each subject in each hemisphere. The order of the hemisphere to be stimulated (left or right) was counterbalanced across subjects and within each experiment with a rest period between the two sessions.

Subjects were seated in front of a computer monitor with a custom-made chin rest fixed to a coil holder. They were also asked to wear a neck brace to further help position their head firmly and they wore noise-cancellation headphones in their ears. Sounds were controlled for amplitude (recorded at -12 dB and played at half of the computer's maximum volume) and duration (5 s). The typing sound consisted of 15 keys being typed, the tearing paper sound of three tears to a paper, the walking sound of nine steps and the thunder sound of two rolling thunders. For the hand-action sound, half of the subjects heard the typing sound while the other half heard the tearing paper sound. The timing of the TMS pulse delivery varied across trials to prevent predictability. Thus, the TMS pulse was delivered at 2.5, 3.0, 3.5 or 4.0 s after the onset of the stimulus. Each sound was followed by 3 s of silence. Participants were explicitly told that they would hear a typing sound or a tearing paper sound, a walking sound, and a thunder sound, and to listen to the sound while focusing on a fixation cross on the computer monitor. Sixty randomly presented trials were run for each subject, with 20 from each condition (20 tearing paper or 20 typing, 20 walking, 20 thunder).

Peak-to-peak amplitudes of the MEPs were measured and mean averages were calculated for each of the three conditions. MEPs 2 SD away from the mean of each subject's data were excluded from the analysis. On average, two out of 60 MEPs recorded from each hand of a subject were excluded on this basis. Next, because MEP size is known for its large interindividual variability (Rossini & Rossi, 1998), MEP size was normalized in order to make responses comparable across subjects. Normalization was calculated by taking the percentage change in the mean MEP size for each of the two experimental conditions from the mean MEP size for the control condition. Thus, for each subject the mean MEP size for an experimental condition (e.g. leg sound) was divided by the mean MEP size for the control condition (thunder), multiplied by 100, and then subtracted from 100. Furthermore, subjects whose mean data for each condition were >2 SD away from the average mean for each condition were excluded from the analysis. Three subjects (two females, one male) were excluded on this basis. Data were analysed using repeated-measures ANOVA with two between-subject variables (sex: male or female; hand sound: typing or tearing) and two within-subject variables (hemisphere: left or right; sound type: hand or leg). To directly see whether larger MEPs are obtained when subjects listened to hand stimuli as compared to leg stimuli, two planned comparisons were also conducted, comparing the hand stimuli to the leg stimuli for each hemisphere. Following the study, subjects were questioned on whether or not they mentally imagined the heard actions. None of the subjects reported mentally imagining the actions throughout the experiment.

Results

All subjects completed the session without problems. On average, MT for the left and right hemisphere was found to be 58 and 57% of maximum stimulator output, respectively.

We predicted that we would find larger MEPs when subjects listened to hand action sounds during stimulation of the left hemisphere primary motor hand area. Our data support this prediction. As Fig. 1 indicates, the interaction between the hemisphere stimulated and the stimulus listened to was significant ($F_{1,17} = 5.50$, $P < 0.05$). A planned comparison indicated that, when the left hemisphere was stimulated, hand action sounds yielded significantly bigger MEPs than leg action sounds ($F = 9.87$, $P < 0.01$). By contrast, a second planned comparison indicated that, when the right hemisphere was stimulated, no significant difference was seen between the sound stimuli. Further, the hand action sounds yielded bigger MEPs in the left hemisphere than in the right hemisphere ($F = 9.7$, $P < 0.01$). By contrast, the leg action sounds did not yield significantly different facilitations in the two hemispheres ($F = 0.001$, $P = 0.97$). Mean MEPs for each

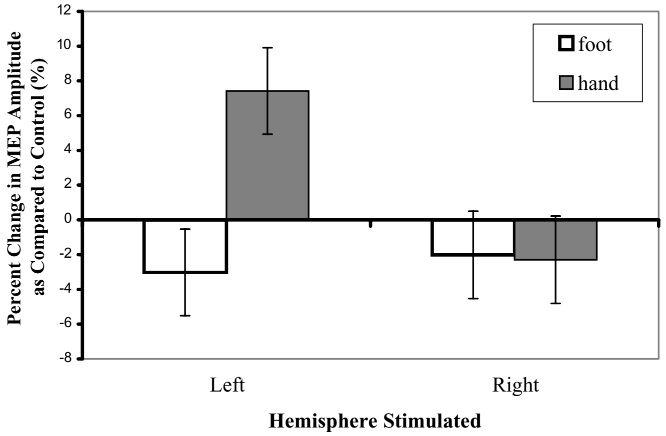

FIG. 1. Mean percentage change in MEP amplitude from control trials while listening to the hand action sound (typing or tearing paper) or the leg action sound (walking) when the left or right primary motor cortex hand area was stimulated. The left hemisphere was especially sensitive to stimulus type, showing significantly larger MEPs to hand action sounds than to leg action sounds. However, when the right hemisphere was stimulated, no significant difference was seen between the sound stimuli.

condition during left hemisphere stimulation of a sample subject are shown in Fig. 2.

One might wonder whether the left hemisphere corticospinal facilitation to the manual action sounds was driven by the relationship of typing to language. However, a *post hoc* means comparison showed that the difference between the hand action sounds (typing or tearing paper) in the left hemisphere was not significant ($F = 0.0640$, $P = 0.802$). In fact the tearing paper sound yielded a larger mean percentage change in MEPs as compared to control than did the typing sound: 8.05 and 6.74%, respectively. Thus, the left hemisphere lateralization in corticospinal facilitation while listening to bimanual action sounds cannot be accounted for by spurious factors such as the association of the sound with language, number of repetitions of the sounds, or hand preference.

Discussion

Our results indicate that the human mirror system may have different ways of coding actions in each hemisphere. In the left hemisphere, actions are coded through auditory, visual and motor components, whereas in the right hemisphere action coding seems to occur only via the visual and motor channels. Thus, the coding in the left hemisphere contains all the contents of an action. This greater number of modalities available selectively to the left hemisphere may have allowed more abstract representations of actions in this hemisphere. Abstraction in the left hemisphere human mirror system makes it well suited for facilitating the emergence of language (Hauser *et al*., 2002).

One may wonder whether the left hemisphere facilitation observed here simply reflects the use of stimuli that are over-learned meaningful actions. There is data, particularly from the apraxia literature, that indicates that over-learned meaningful actions are more strongly lateralized to the left hemisphere (Heilman & Valenstein, 2003). On the other hand, language also consists of a set of over-learned meaningful actions (i.e. actions made by the mouth for speech or by the hand for sign language). Meaningful action coding, as a property of the left hemisphere, could be reflected in both language and praxis. Therefore, while both hemispheres may be capable of action processing through (at least) the visuo-motor channels (Aziz-Zadeh *et al*., 2002a; Aziz-Zadeh *et al*., 2002b; Molnar-Szakacs *et al*., 2002), the left hemisphere may additionally be more sensitive to meaningful actions. Perhaps the sensitivity to meaning and the additional multimodality and/or abstraction of the neurons in this hemisphere may have been necessary for language development.

It is interesting that no such lateralization was observed for auditory mirror neurons in macaques; auditory mirror neurons were found in both the right and left hemisphere without obvious differences in frequency (C. Keysers, personal communication). This indicates that such lateralization seems to arise later in evolution, maybe in great apes (Cantalupo & Hopkins, 2001) if not in humans.

While we can not rule out the effects of sound frequency on the observed left hemisphere facilitation, it seems unlikely that this factor alone could account for the selective facilitation of both varieties of hand action sounds over the control stimuli. With regard

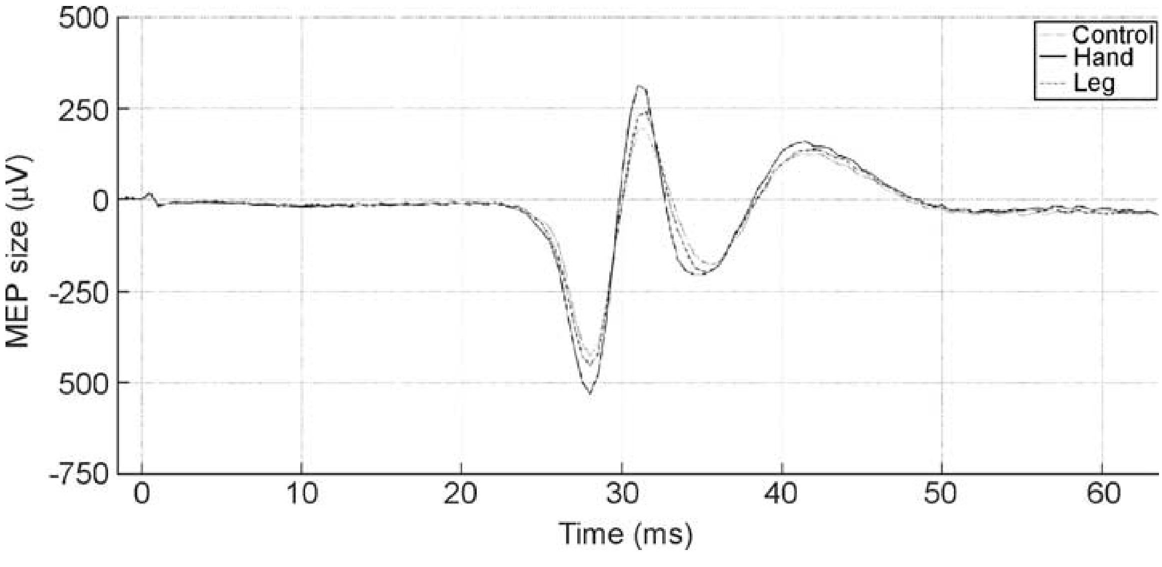

FIG. 2. Mean MEPs for each condition for a sample subject. The average MEP while listening to the hand action sound (typing) is larger than while listening to the leg action sound or the control sound. On the time axis, zero indicates the time of TMS onset.

to the frequency of repetition of the sounds, both the walking sound and the typing sound consisted of several repetitions, and thus serve as controls for one another. Similarly, the tearing paper sound and the thunder sound had similar repetition frequencies. Finally, a *post hoc* means comparison exploring differences between the tearing paper and typing sounds was not significant. This indicates that the number of repetitions of the sound is not likely to be a factor in evoking motor facilitation.

There have been a few studies exploring the asymmetry of cortical excitability of the motor system. While previous literature suggests that there may be a spinal asymmetry in excitability (Marchand-Pauvert *et al*., 1999), cortical asymmetry has been found with paired-pulse TMS techniques (Civardi *et al*., 2000). To minimize the possibility of an effect of an asymmetry in cortical excitability, we normalized MEPs separately for each hemisphere. That is, in each hemisphere we compared the percentage difference of MEP size in experimental conditions to control conditions. Thus it seems unlikely that a difference in hemispheric cortical excitability could strongly influence our results.

Is left hemisphere specialization for action sounds specific for bimanual actions or might it be generalized to sounds made by other body parts? The position of the leg representation in the primary motor cortex (on the midline and deep in the cortex) makes it difficult to explore hemispheric differences using TMS over this area. Furthermore, given the stronger bilateral control for the leg one may not expect hemispheric differences for this effector. However, other brain imaging techniques may be better suited for exploring this question in the future.

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Abbreviations

FDI, first dorsal interosseus; fMRI, functional magnetic resonance imaging; MEP, motor evoked potential; MT, motor threshold; TMS, transcranial magnetic stimulation.

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