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Cortical Mechanisms of Human Imitation

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How does imitation occur? How can the motor plans necessary for imitating an action derive from the observation of that action? Imitation may be based on a mechanism directly matching the observed action onto an internal motor representation of that action ("direct matching hypothesis"). To test this hypothesis, normal human participants were asked to observe and imitate a finger movement and to perform the same movement after spatial or symbolic cues. Brain activity was measured with functional magnetic resonance imaging. If the direct matching hypothesis is correct, there should be areas that become active during finger movement, regardless of how it is evoked, and their activation should increase when the same movement is elicited by the observation of an identical movement made by another individual. Two areas with these properties were found in the left inferior frontal cortex (opercular region) and the rostral-most region of the right superior parietal lobule.

Imitation has a central role in human development and learning of motor, communicative, and social skills (*1*, *2*). However, the neural basis of imitation and its functional mechanisms are poorly understood. Data from patients with brain lesions suggest that frontal and parietal regions may be critical for human imitation (*3*) but do not provide insights on the mechanisms underlying it.

Models of imitation based on instrumental learning, associative learning, and more complex cognitive processes have been proposed (*1, 4*). Because imitation is not a unitary phenomenon (*2*), it is possible that different imitative behaviors, subsumed under this name, result from different mechanisms. The ability to copy elementary actions, however, should be based on simple neural mechanisms. In keeping with this concept, the ability to imitate facial and manual gestures can be demonstrated in infants even a few days or hours old (*5*). The basis of this type of imitation might involve a "resonance" mechanism (*6*) that directly maps a pictorial or kinematic description of the observed action onto an internal motor representation of the same action. This proposal is supported by the recent discovery in the premotor cortex of the macaque monkey (area F5) of neurons that fire both when the monkey performs an action and when it observes an individual making a similar action (*7*). Thus, a comparable direct matching mechanism between the observed and executed action is a reasonable candidate for human imitation.

The direct matching hypothesis predicts that the areas where matching occurs must contain neurons that discharge during action execution regardless of how action is elicited and that at least a subset of them should receive input representing the action they encode. Cortical areas endowed with a matching mechanism should, therefore, have motor properties, and, more importantly, they should become more active when the action to be executed is elicited by the observation of that action.

To assess whether such a mechanism exists, we used functional magnetic resonance imaging (fMRI), which allows the in vivo study of human brain functions. The paradigm involved three observation conditions and three observation-execution conditions. In the observation-execution conditions, imitative and nonimitative behavior of simple finger movements was compared. In an imitative condition, participants had to execute the observed finger movement. In the two nonimitative conditions, participants had to execute the same movement in response to spatial or symbolic cues (*8*) (Fig. 1).

The imitation task (*9*, *10*) produced reliably larger signal intensity (df = 66, $t = 5.08$, $P < 0.0125$, corrected for multiple spatial comparisons) when contrasted, either individually or together, with the other two observation-execution tasks. This effect was observed in three areas: the left frontal operculum, the right anterior parietal region, and the right parietal operculum (Fig. 2). In the first two areas, activation was also present during all three observation tasks. During all scans the participants knew that the task was either to move a finger or to refrain from moving it. Thus, the mental imagery of their finger (or of the finger movement) should have been

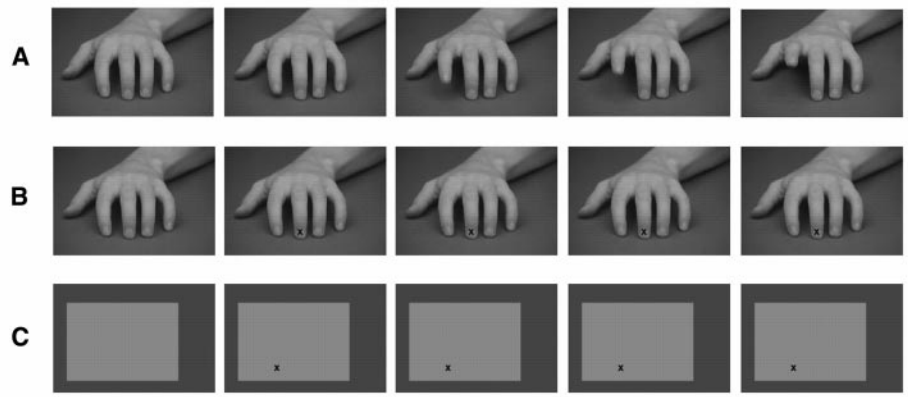

Fig. 1. Sequence of pictures shown to participants for each of the three types of stimuli. The pictures do not show the participants' hands. Each trial in the sequence lasted 3 s. (**A**) Animated hand (only index finger trials are displayed). (**B**) Static hand (only middle finger trials are displayed). (**C**) Geometric figure (only index finger trials are displayed). The tasks were as follows. *Observation conditions*: (i) Action. An animated hand was displayed on the computer screen. The index or the middle finger of the animated hand was lifted at random. The instruction was to observe only. (ii) Static hand with a cross. A static hand was displayed on the screen, and a cross appeared on the index or the middle finger at random. The instruction was to observe only. (iii) Geometric figure. A gray rectangle was displayed, and a cross appeared on the left or right side of it at random. The instruction was to observe only. *Observation-execution conditions*: (i) Imitation. An animated hand was displayed on the computer screen. The index or the middle finger of the animated hand was lifted at random, and the instruction was to imitate the movement with the right hand. (ii) Symbolic instruction. A static hand was displayed on the screen, and a cross appeared on the index or the middle finger at random. The instruction was to lift the corresponding finger of the right hand in response to the cross. (iii) Spatial instruction on geometric figure. A gray rectangle was presented and a cross appeared on the left or right side of it at random. The instruction was to lift the right index finger if a left cross appeared and the right middle finger if a right cross appeared.

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present even during simple observation. This background activity was potentiated when the stimulus to be imitated was presented. These findings indicate, therefore, that the left frontal operculum (area 44) and the right anterior parietal cortex (PE/PC) have an imitation mechanism as postulated by the direct mapping hypothesis.

There are several reasons to expect that, if a direct mapping for manual imitation does exist, it should involve Broca's area (area 44). First, area 44 is one of the relatively few cortical areas where distal movements (the type of movements imitated in this experiment) are represented in humans (*11*). Second, area 44 is considered the human homolog of monkey area F5 (*12*), in which an action observation-execution matching system exists (*7*). Third, Broca's area is the motor area for speech, and learning by imitation plays a crucial role in language acquisition. Fourth, as argued previously (*13*), language perception should be based on a direct matching between linguistic material and the motor actions responsible for their production. Broca's area is the most likely place where this matching mechanism might occur.

Activation in the PE/PC area in monkeys is essentially related to the elaboration of proprioceptive information. Neurons from area PE are active during passive joint rotation, deep tissue pressure, and active arm movements (*14*, *15*). In humans, positron emission tomography (PET) experiments have demonstrated that there are different activation patterns when participants observe pantomimes of complex actions to understand their meaning as opposed to memorizing and repeating them. In the first case, there is an activation of the left inferior frontal lobe, mostly area 45 (*16, 17*), but in the latter, the activation is predominantly parietal, more prominent on the right (*16*). On the basis of the physiological properties of area PE/PC neurons and these last data, a plausible interpretation of the parietal activation during imitation is that a kinesthetic copy of the movement is formed in the right parietal lobe during movement observation. This copy, indicating the final and possibly intermediate joint positions is then used during action execution.

If this is so, why are two areas involved in imitation, and what is the difference between the activation in the parietal and Broca's areas? We propose that the inferior frontal area describes the observed action in terms of its motor goal (for example, lift the finger) without defining the precise details of the movement. In contrast, the parietal lobe area codes the precise kinesthetic aspects of the movement (for example, how much the finger should be lifted). This hypothesis is based on data showing that F5 neurons code the general goal of a movement and not the precise movement details (*7*), whereas PE neurons code a proprioceptive storage of limb position (*14*). Thus, although both areas will collaborate in action imitation, the more prevalent influence will be of the left frontal cortex (to perform the task) or of the right parietal cortex (to repeat the exact movement), according to the task request.

An immediate question that the direct matching mechanism of imitation raises is how an individual may preserve the sense of self during action observation, given the shared motor representation between the "actor" of the movement and the "imitator." The activation in the parietal operculum is probably relevant to this question. The parietal operculum is a sensory area, and its activity here most likely reflects reafferent signals

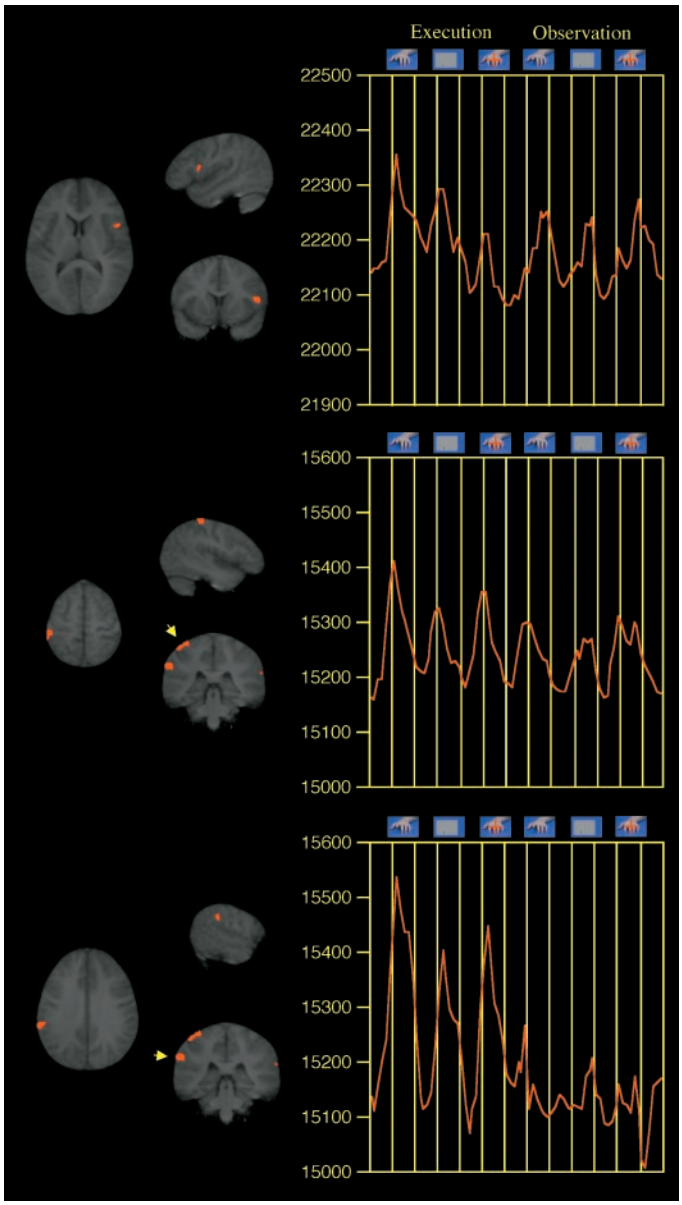

Fig. 2. Areas of significant signal intensity (in red) changes and relative time series. (**Top**) Activation and relative time series in the left frontal operculum. Talairach coordinates of peak (t = 5.86) activity: x = −50, y = 12, z = 12. Cluster size = 90 voxels. The left frontal area is presented in transverse, sagittal, and coronal views of the Talairach-compatible brain MR atlas (*10*). The time series is the average time series of all four runs in all 12 participants participating in the study. Thus, each data point in the displayed time series is the average of 48 data points. The order of tasks was counterbalanced across participants in the real experiment but is displayed as a fixed order in this figure. The time series is composed of seven rest periods alternating with six task periods. Each task period is divided by a vertical yellow line. The first three task periods correspond to the observation-execution tasks and the last three task periods correspond to the observation tasks. The small pictures on top of each task period represent the type of stimulus presented and are used here for display purpose only. The hand with the lifted finger corresponds to the animated hand [(A) of Fig. 1], the geometric figure corresponds to the geometric figure [(C) of Fig. 1], and the hand with the red cross on it corresponds to the static hand [(B) of Fig. 1]. In the real experiment, the cross was black and small and was located on the middle or index finger (Fig. 1). The values displayed in the time series are fMRI signal intensity values rescaled by the smoothing process. (**Center**) Activation and relative time series in the right anterior parietal region at the intersection between postcentral sulcus and intraparietal sulcus (indicated by the yellow arrow in the coronal view). Talairach coordinates of peak (t = 5.89) activity: x = 37, y = −40, z = 57. Cluster size = 137 voxels. (**Bottom**) Activation and relative time series in the right parietal operculum (indicated by the yellow arrow in the coronal view). Some activated voxels in the contralateral parietal operculum are also visible in the coronal view. Talairach coordinates of peak (t = 7.32) activity: x = 58, y = −24, z = 32. Cluster size = 108 voxels. Voxel size = 2 mm by 2 mm by 2 mm.

associated with action. Note also that the activation is mostly lateralized to the right hemisphere and that lesions to the right inferior parietal lobule are typically associated with body schema disorders (*18*). Enhancing brain activity of this area during action production can be a computationally simple way to preserve body identity ("it is my body that is moving") during imitation (*19*).

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8. Two recent behavioral studies demonstrated that movement observation strongly affects movement execution in a paradigm similar to the one adopted here (M. Brass, H. Bekkering, A. Wohlschlager, W. Prinz, *Brain Cogn.*, in press; M. Brass, H. Bekkering, W. Prinz, *Acta Psychol.*, in press). In both of these studies, as in this imaging study, a "mirror" configuration (right hand imitation of left hand action) was selected because it has been repeatedly shown that there is a natural tendency to imitate in the mirror configuration [H. Head, *Brain*, **43**, 87 (1920); N. C. Kephart, *The Slow Learner in the Classroom* (Charles Merrill, Columbus, OH, 1971); W. N. Schofield, *Q. J. Exp. Psychol.* **28**, 571 (1976)].
9. A total of 16 participants were studied, following the UCLA Human Subject Protection Committee guidelines. Four participants belonged to a pilot study, which was performed to evaluate the feasibility of the experiment in a fMRI setting. The four participants in the pilot study were three males and one female, and their mean age was 37.75 years (±15.84). The 12 participants in the experiment were nine males and three females, and their mean age was 25.42 years (±5.8). All participants were right-handed, as assessed with a questionnaire that was modified from the Edinburgh Handedness Inventory [R.C. Oldfield, *Neuropsychologia* **9**, 97 (1971)], and had no neurological abnormalities identified at the neurological examination that was performed just before the scanning procedure.
10. We used an echo planar T_2*-weighted gradient echo sequence [repetition time (TR) = 4000 ms; echo time (TE) = 70 ms; flip angle = 90°; 64 by 64 volume element (voxel) matrix; 26 axial slices; 3.125-mm in-plane resolution; 4-mm thickness; interslice gap (skip) = 1 mm)]. We also acquired a coplanar high-resolution echo planar imaging (EPI) volume (TR = 4000 ms; TE = 54 ms; flip angle = 90°; 128 by 128 voxel matrix; 26 axial slices; 3.125-mm in-plane resolution; 4-mm thickness; skip = 1 mm), to obtain anatomical data on our participants. The software program MacProbe [E. Zaidel and M. Iacoboni, *Brain* **119**, 2155 (1996)] was used for stimulus presentation. Four fMRI scans of 5 min and 20 s each were performed on every participant. The six tasks were alternated with seven rest periods. Each task or rest period lasted 24 s, except for the last rest period, which lasted 36 s. Each trial lasted 3 s. Thus, each task period comprised eight trials. The task order was counterbalanced across participants. In-plane Gaussian filtering was applied to produce a final image resolution of 8.7 mm by 8.7 mm by 8.6 mm. Image registration for each participant was performed by aligning the functional volumes to the coplanar high-resolution EPI volume with a rigid-body linear registration algorithm [R. P. Woods, S. T. Grafton, C. J. Holmes, S. R. Cherry, J. C. Mazziotta, *J. Comput. Assisted Tomogr.* **22**, 139 (1998)]. Image registration for the group of participants was performed with fifth-order polynomial nonlinear warping [R. P. Woods, S. T. Grafton, J. D. G. Watson, N. L. Sicotte, J. C. Mazziotta, *J. Comput. Assisted Tomogr.* **22**, 153 (1998)] of each participant's images into a Talairach-compatible brain magnetic resonance (MR) atlas [R. P. Woods, M. Dapretto, N. L. Sicotte, A. W. Toga, J. C. Mazziotta, *Hum. Brain Mapp.* **8**, 73 (1999)]. Statistical analysis was performed with analysis of variance (ANOVA) [R. P. Woods, M. Iacoboni, S. T. Grafton, J. C. Mazziotta, in *Quantification of Brain Function Using PET*, R. Myers, V. Cunningham, D. Bailey, T. Jones, Eds. (Academic Press, San Diego, CA, 1996), pp. 353–358]. Participants (n = 12), fMRI scans (n = 4), task (n = 2: observation and observation-execution), and stimuli (n = 3: animated hand, static hand, and geometric figure) were included in the ANOVA, whereas rest periods were excluded. Because of the "blurred" hemodynamic response, the six brain volumes acquired per task period cannot be considered independent observations. Thus, we used the sum of the signal intensity at each voxel throughout each task period as the dependent variable. To account for the delayed hemodynamic response [R. S. Menon and S.-G. Kim, *Trends Cogn. Sci.* **3**, 207 (1999)], we excluded the first brain volume of each task period and included the first brain volume of the following rest period. The statistical threshold, estimating variance at each voxel, was corrected for spatial multiple comparisons [K. J. Worsley *et al.*, *Hum. Brain Mapp.* **4**, 58 (1996)]. Although cluster size is reported here, cluster size was not used in computing statistical significance; that is, even a single activated voxel would be statistically valid. The alpha level was also Bonferroni corrected for multiple comparisons. Given that we were interested in the cortical correlates of imitation, only cortical regions with motor properties were considered. Thus, our search region of interest was limited to the cerebral cortex of the frontal and parietal lobes.
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Heterozygous Germ Line *hCHK2* Mutations in Li-Fraumeni Syndrome

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The *hCHK2* gene encodes the human homolog of the yeast Cds1 and Rad53 G_2 checkpoint kinases, whose activation in response to DNA damage prevents cellular entry into mitosis. Here, it is shown that heterozygous germ line mutations in *hCHK2* occur in Li-Fraumeni syndrome, a highly penetrant familial cancer phenotype usually associated with inherited mutations in the *TP53* gene. These observations suggest that *hCHK2* is a tumor suppressor gene conferring predisposition to sarcoma, breast cancer, and brain tumors, and they also provide a link between the central role of p53 inactivation in human cancer and the well-defined G_2 checkpoint in yeast.

Li-Fraumeni syndrome (LFS) is a rare familial multicancer syndrome characterized by the occurrence of sarcomas, breast cancer, brain tumors, leukemia, and adrenal cortical tumors in multiple relatives (*1*). In most cases, LFS results from inheritance of a mutant *TP53* allele, followed by somatic loss of the remaining wild-type allele, which thus constitutes the primary initiating event leading to cancer (*2, 3*). The central role of *TP53* mu-