

Observing complex action sequences: The role of the fronto-parietal mirror neuron system

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A fronto-parietal mirror neuron network in the human brain supports the ability to represent and understand observed actions allowing us to successfully interact with others and our environment. Using functional magnetic resonance imaging (fMRI), we wanted to investigate the response of this network in adults during observation of hierarchically organized action sequences of varying complexity that emerge at different developmental stages. We hypothesized that fronto-parietal systems may play a role in coding the hierarchical structure of object-directed actions. The observation of all action sequences recruited a common bilateral network including the fronto-parietal mirror neuron system and occipito-temporal visual motion areas. Activity in mirror neuron areas varied according to the motoric complexity of the observed actions, but not according to the developmental sequence of action structures, possibly due to the fact that our subjects were all adults. These results suggest that the mirror neuron system provides a fairly accurate simulation process of observed actions, mimicking internally the level of motoric complexity. We also discuss the results in terms of the links between mirror neurons, language development and evolution.

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Introduction

Neurons with mirror properties have been described in both area F5 of the premotor cortex and in parietal area PF of the macaque brain (Rizzolatti and Craighero, 2004). These visuomotor

neurons discharge both when the monkey performs an action and when it observes another individual perform a similar action (di Pellegrino et al., 1992; Gallese et al., 1996, 2002; Rizzolatti et al., 1996a; Ferrari et al., 2001, 2003; Umiltà et al., 2001; Rizzolatti and Craighero, 2004; Fogassi et al., 2005). In addition, a subset of the premotor mirror neurons are able to represent actions even when the final part of the action is unseen (Umiltà et al., 2001). Parietal mirror neurons have the special property of coding motor acts as belonging to an action sequence, predicting the intended goal of a complex action (Fogassi et al., 2005). Thus, area F5 of the ventral premotor cortex, and area PF of the inferior parietal lobule in the monkey form a fronto-parietal mirror neuron system critical to action understanding and intention attribution (Rizzolatti et al., 2001; Rizzolatti and Craighero, 2004; Fogassi et al., 2005).

Evidence suggests that the human homologue of monkey premotor area F5 is Brodmann area 44 (BA44) (VonBonin and Bailey, 1947; Petrides and Pandya, 1997; Amunts et al., 1999; Tomaiuolo et al., 1999) located within the sulcal borders of the pars opercularis of the inferior frontal gyrus (IFG), in probabilistic terms (Amunts et al., 1999; Mazziotta et al., 2001). Parallel evidence suggests that area PF in the monkey corresponds to the rostral part of the human inferior parietal lobule (IPL) (VonEconomo and Koskinas, 1925; Rizzolatti and Matelli, 2003; Rizzolatti and Craighero, 2004). Thus, a circuit for action representation in humans is formed by the posterior portion of the IFG and adjacent ventral premotor cortex and by the rostral part of IPL (Rizzolatti and Craighero, 2004).

A large number of neuroimaging studies have now shown that the human fronto-parietal mirror neuron system is engaged during the mere observation of simple finger movements (Iacoboni et al., 1999; Nishitani and Hari, 2000; Hermsdörfer et al., 2001; Molnar-Szakacs et al., 2005; Aziz-Zadeh et al., 2006), pantomimes (Decety

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et al., 1997; Johnson-Frey et al., 2005) and object-directed actions (Fadiga et al., 1995; Grafton et al., 1996; Rizzolatti et al., 1996b; Hari et al., 1998; Buccino et al., 2001, 2004; Perani et al., 2001; Johnson-Frey et al., 2003; Manthey et al., 2003; Iacoboni et al., 2005). Furthermore, we have recently shown that the frontal mirror neuron region is also involved in understanding the intentions behind the actions of others (Iacoboni et al., 2005). Thus, the mirror neuron system in humans appears to subserve both the ability to understand which actions are appropriate to act on an object and the mechanisms by which we understand the intentions behind the actions of others.

Neuroimaging studies of language function and studies of sensory-motor integration have pointed out links between the mirror neuron system and the brain regions involved in linguistic

processing (Rizzolatti and Arbib, 1998; Arbib, 2005). More recently, we have proposed that parallel functional segregation within Broca's area during language and motor tasks may reflect similar computations used in both language and motor control (Molnar-Szakacs et al., 2005). Even before the discovery of mirror neurons, developmental investigations, psycholinguistic research, cross-species comparison, and neuroscientific studies had shown behavioral and neural links between the emergence of hierarchical processing in action and hierarchy in linguistic grammar (Greenfield, 1978, 1991; Greenfield and Westerman, 1978; Greenfield and Dent, 1982). This body of research on infants and children has shown a systematic developmental progression toward the ability to use increasingly complex strategies in object combination sequences (Greenfield et al., 1972; Goodson and Greenfield, 1975;

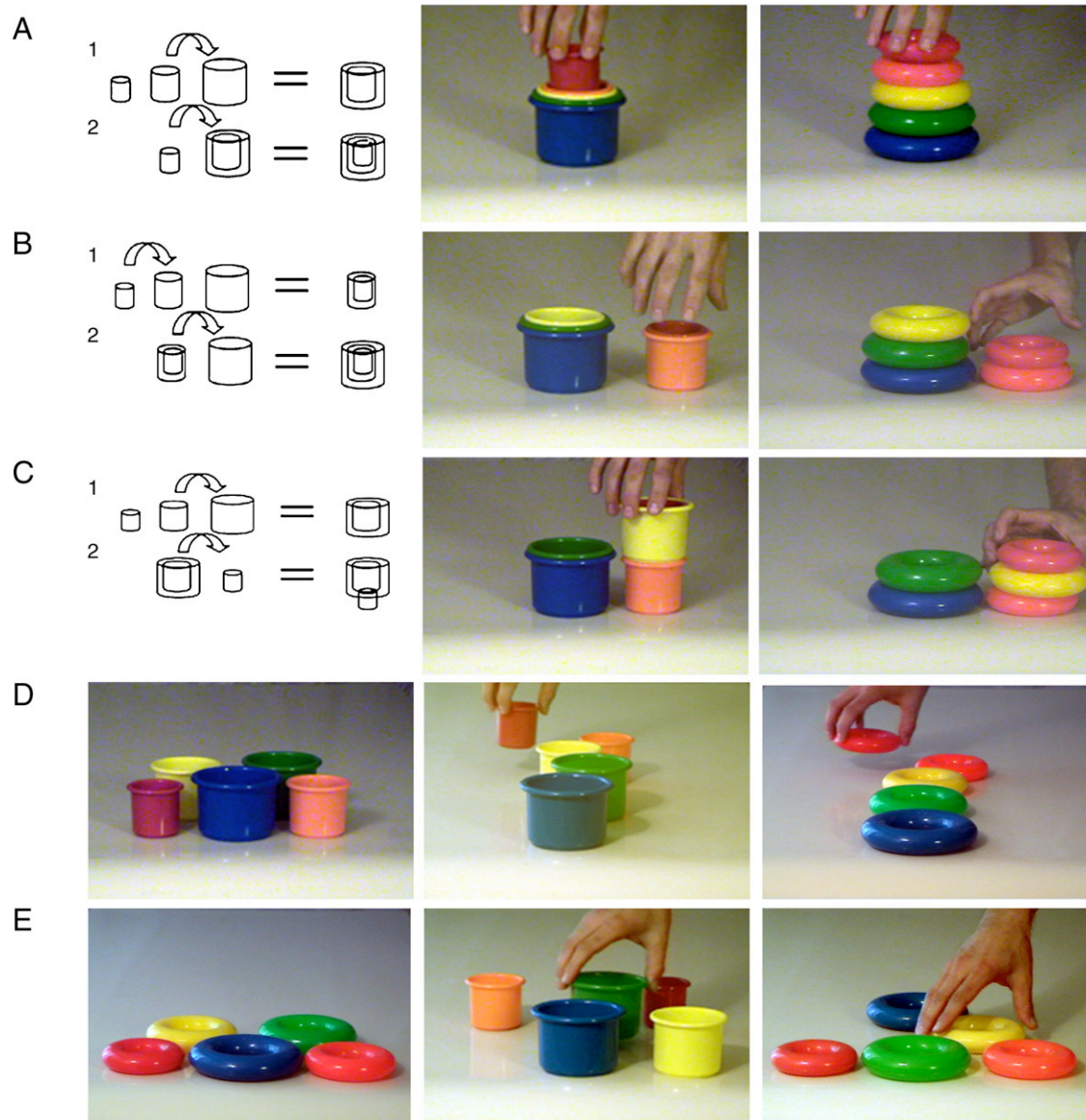


Fig. 1. Experimental conditions showing strategies for combining seriated cups in diagrammatical form [adapted from Greenfield et al. (1972)] and still images taken from the corresponding stimulus video clips showing both seriated cups and stacking rings: (A) seriated pot, (B) seriated subassembly and (C) stacked subassembly conditions. Still images illustrating the starting position and the final position of the objects: (D) size-ordered control, (E) random movement control. The arrangement of objects at the start of a clip was the same for experimental (A–C) and control (D–E) conditions. For more information, please see Methods.

Greenfield and Schneider, 1977). In the earliest developmental period, action strategies used by children to combine objects progress through three stages of developmental complexity: pairing, pot and subassembly. In pairing, the child is limited to combining two objects together. In the pot strategy, one object serves as a common receptacle (the “pot”) and all other objects are placed in (or on) this pot. In the subassembly method, two or more objects are first combined with each other (e.g., one cup placed in another) and then moved as a single unit to combine with an additional object (for example a nest of two cups could be placed into a third cup).

After observing a demonstration in which a series of five cups of graduated size is seriated, one inside another by means of the subassembly method (see below), infants under 16 months of age can combine objects by pairing (Greenfield et al., 1972). The pot method, which emerges at 20 months of age, involves placing two or more active or agentive cups in or on a passive recipient cup, which serves as the pot. This strategy requires a more complex understanding of the hierarchical relationships between component elements of a structure. (See an example of the pot strategy in Fig. 1A.) The hierarchically most complex subassembly strategy emerges at 36 months of age. The essence of subassembly is that two or more cups are combined into a stack or subassembly and then moved as a single unit into or on another cup. This feature of subassembly contrasts with the pot strategy in which a single object is always the operative or moving unit (Greenfield et al., 1972). The other aspect of structural complexity in the subassembly strategy is that the object or passive cup in one combination becomes the active cup in the next. (See examples of the subassembly strategy in Figs. 1B and C). Role change from passive to active in the subassembly strategy contrasts with the pot strategy in which each cup plays but a single role in the action sequence. The increased structural and combinatorial complexity of the subassembly strategy results in increased cognitive complexity, as evidenced by its relatively later emergence in development.

Remarkably, the three action strategies are acquired in the same developmental order – (1) pairing, (2) pot and (3) subassembly – as the corresponding linguistic grammatical structures—(1) simple, (2) coordinate, and (3) complex (Greenfield et al., 1972; Greenfield, 1978, 1999; Greenfield and Westerman, 1978).

Grossman (1980) used evidence from aphasic patients to suggest that Broca’s area is the common neural substrate for processing hierarchy in both language and action. He found that Broca’s aphasics who lack hierarchical organization in their syntactic production were also impaired in recreating hierarchically organized tree structures used by Greenfield and Schneider (1977). In contrast, fluent aphasics, who have hierarchically organized (but semantically empty) speech were able to reproduce the hierarchical structure of the models (Grossman, 1980).

Hierarchically organized sequential operations are fundamental to both language and action, leading Greenfield (1991) to propose that language and motor abilities share cognitive resources and a homologous neural substrate (Broca’s area). Although there is now a large body of neuroimaging evidence showing mirror neuron system activity in the human brain during action observation, thus far, there have been no studies linking the mirror neuron system to processing hierarchical complexity in observed action sequences. We adopted the different hierarchically organized structures described by the developmental model (Greenfield et al., 1972) as stimuli in this fMRI study of action observation to investigate

the role of the fronto-parietal human mirror neuron system in representing observed complex action sequences.

Methods

Subjects

Twelve subjects (six males) with a mean age of 27.8 years (range 22–37) were recruited and compensated for their participation. Subjects gave written informed consent according to the guidelines of the UCLA Institutional Review Board. All participants were screened to rule out medication use, head trauma, history of neurological or psychiatric disorders, substance abuse, or other serious medical conditions. All subjects were right-handed according to a modified Edinburgh Handedness Questionnaire (Oldfield, 1971).

Image acquisition

Images were acquired using a Siemens Allegra 3.0 T MRI scanner. Two sets of high-resolution anatomical images were acquired for registration purposes. We acquired an MP-RAGE structural volume (TR=2300, TE=2.93, flip angle=8°) with 160 sagittal slices, each 1 mm thick with 0.5 mm gap and 1.33 mm×1.33 mm in-plane resolution. For registration purposes we also acquired a T2-weighted EPI co-planar volume (TR=5000, TE=33, flip angle=90°) with 36 transverse slices covering the whole brain, each 3 mm thick with 1 mm gap, a 128×128 matrix and an in-plane resolution of 1.5 mm×1.5 mm.

Each functional run involved the acquisition of 113 EPI volumes (gradient-echo, TR=4000, TE=25, flip angle=90°), each with 36 transverse slices, 3 mm thick, 1 mm gap, and a 64×64 matrix yielding an in-plane resolution of 3 mm×3 mm. A functional run lasted 7 min and 32 s, and each subject completed 3 functional runs.

Stimuli and task

The entire stimulus set for this study consisted of twenty digital video clips recorded using a MiniDV Handycam DCR-TRV 38 (Sony Corporation). iMovie 3.0.3 (Apple Computer, Inc.) was used to edit each clip to a uniform length of 10 s. Half of the stimulus set, ten clips, depict manual object manipulation sequences of varying complexity using seriated cups, while ten other clips show the same sequences using stacking rings as the target objects (for examples of the stimulus objects, see Fig. 1). We used two different sets of objects in our stimulus set to avoid the subjects’ habituation to the stimulus material. Each clip used the same five seriated cups or stacking rings filmed against a white background. The objects were matched for relative size and color across the two types of objects (in order of increasing size: blue, green, yellow, orange and red). The starting position of the objects in all the clips was always the same (Figs. 1D, E). All clips contained a sequence of four movements, to ensure that the number of times the hand contacted the objects was constant across conditions. Furthermore, in each stimulus video, the onset of the movement coincided with the start of the video, and the video terminated at the end of the sequence of movements. In this way, all videos contain the same amount of movement time.

Composing the set of 10 video clips showing seriated cups, there were 2 video clips for each of the following five conditions:

seriated pot, seriated subassembly, stacked subassembly, size-ordered and random manipulation control. These same conditions were also filmed using the stacking rings (5 conditions \times 2 clips each = 10 video clips). Each video clip consists of a sequence of four movements during which a right hand is visible, and moves one object, or a subassembly of objects. In the seriated pot condition, a single object at a time is moved into another, larger object to form a size-ordered structure (Fig. 1A). In the seriated subassembly condition, pairs of objects are created and then combined into a more hierarchical size-ordered structure (Fig. 1B). In the stacked subassembly condition, the pairs of objects are combined to form a non-seriated hierarchical stacked structure (Fig. 1C). The developmental sequence of strategies for manipulating objects implies that the subassembly strategy (both stacked and seriated) is ontogenetically and cognitively more complex than the pot strategy (Greenfield et al., 1972). The size-ordered control condition shows the objects being seriated in order of increasing size, without creating a hierarchical structure (Fig. 1D). The random manipulation control condition shows the objects being moved with no obvious strategy, and they do not result in any kind of structure (Fig. 1E).

Subjects were given instructions to watch the video clips carefully, paying attention to the manipulation of objects. The software package Presentation (Neurobehavioral Systems Inc.) was used to present the stimuli through magnet-compatible goggles (Resonance Technology Inc.). During each 7-min 32-s functional run, each of the 20 clips was shown once in a random sequence, starting with a 12-s rest and including 12-s inter-stimulus intervals.

Data processing and statistical analysis

Analysis was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.1, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). After motion correction using the Linear Image Registration Tool (MCFLIRT) (Jenkinson et al., 2002), images were temporally high-pass filtered with a cutoff period of 75 s and smoothed using a 5-mm Gaussian FWHM algorithm in 3 dimensions. The blood oxygen level-dependent (BOLD) response was modeled using a separate explanatory variable (EV) for each of the ten stimulus types. For each stimulus type, the presentation design was convolved with a gamma function to produce an expected BOLD response. The temporal derivative of this time course was also included in the model for each EV. Data were then fitted to the model using FSL's implementation of the general linear model.

Each subject's statistical data were then warped into a standard space based on the Montreal Neurological Institute Talairach-compatible (MNI-152) atlas. We used FLIRT to register the functional data to the atlas space in three stages (Jenkinson et al., 2002). First, functional images were aligned with the high-resolution co-planar T2-weighted image using a 6 degrees of freedom rigid-body warping procedure. Next, the co-planar volume was registered to the T1-weighted MP-RAGE using a 6 degrees of freedom rigid-body warp. Finally, the MP-RAGE was registered to the standard MNI atlas with a 12 degrees of freedom affine transformation.

Higher level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) (Behrens et al., 2003). Z (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.05$ (Worsley et al., 1992; Friston et al., 1994; Forman et al., 1995).

Behavioral experiment

We wished to assess the behavioral complexity of the action sequences in order to better interpret our results. We therefore tested a separate group of twelve normal subjects (7 males) with a mean age of 26.2 years (range 21–31) using a paradigm similar to that described above for the fMRI portion of the study. Nine of the subjects were right handed and two were left handed (1 male, 1 female). Subjects were seated at a table in front of a computer screen on which they were presented with the stimulus videos described above. On either side of the screen, in front of the subject, the seriated cups and stacking rings were arranged in the starting position illustrated in Fig. 1. Subjects were presented with a stimulus video clip and were asked to replicate the object manipulation sequence they had just observed, with the hands always starting and ending from rest in the subject's lap. Each trial was timed using a stopwatch. Reaction times (RT) and errors were recorded. After each trial, the objects were replaced to starting position, and the next video was launched. In the course of a run, each subject was presented with the full set of twenty videos in random order. In this manner, all subjects completed three runs. Videos were fully randomized within each run and across all subjects as in the fMRI portion of the study.

Results

Behavioral results

We tested subjects on three runs of sequential object manipulation in order to collect behavioral data on the 'execution' component of the object manipulation strategies 'observed' in the fMRI. We performed a repeated-measures ANOVA on the task time with the factors: Run (1, 2, 3), Condition (Stacked subassembly, seriated subassembly, Seriated pot, Seriated control, Random control) and Object (Seriated cups, Stacking rings). Significant main effects were followed up with direct t -tests. Statistical significance for the t -tests was set at $P = 0.05$.

The ANOVA revealed a significant main effect of Condition ($F_{4,8} = 26.59$, $P < 0.001$; Stacked subassembly ($M = 8.97$ s) took significantly longer than Seriated subassembly ($M = 7.95$ s; $P < 0.001$) and Seriated pot ($M = 6.86$ s; $P < 0.0001$), but was not different from the control conditions. Seriated subassembly took longer to construct than seriated pot ($P < 0.0001$). Both the Random control ($M = 8.63$ s) and Seriated control ($M = 8.51$ s) conditions showed longer RTs than the Seriated subassembly condition ($P < 0.05$) and the seriated pot condition ($P < 0.0001$), but were no different from one another.

We also found a significant main effect of Run ($F_{2,10} = 13.63$, $P < 0.01$). Run 2 ($M = 8.13$ s) was significantly faster than Run 1 ($M = 9.00$ s; $P < 0.0001$) and in turn Run 3 ($M = 7.41$ s) was significantly faster than both Run 1 ($P < 0.0001$) and Run 2 ($P < 0.0001$). This effect indicates that subjects got faster at performing the task over the course of three runs.

We found no further significant main effects or interactions.

Errors in replication of the observed object manipulation sequences were too few for statistical analysis. The mistakes in construction that we considered to be errors for the purposes of analysis were those manipulations that were not consistent with the appropriate strategy of the particular trial. For example, if a seriated pot sequence was substituted for seriated subassembly, it would be considered an error. However, if the object manipulation was

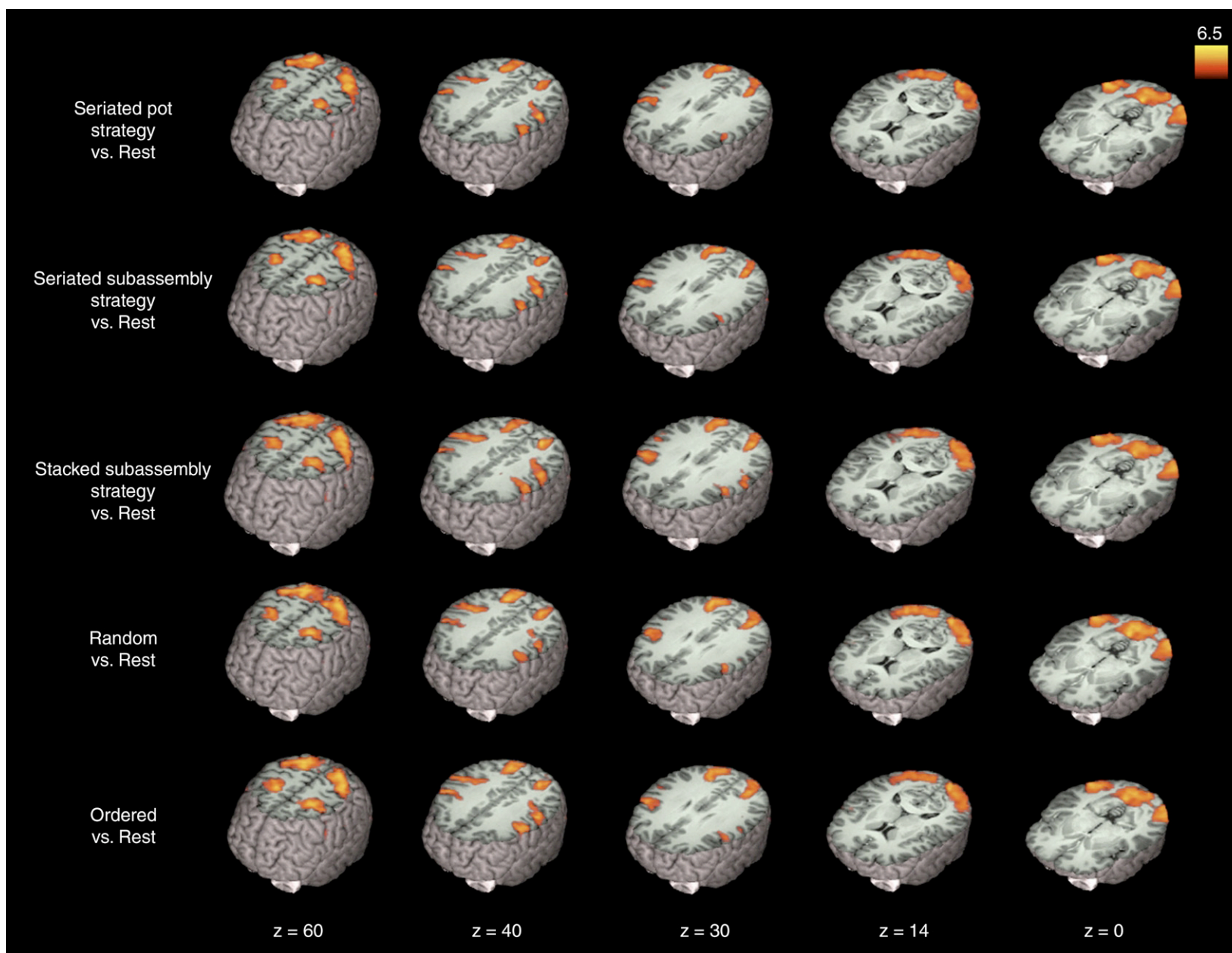


Fig. 2. Signal increases during observation of the five object manipulation conditions (Seriated pot, Seriated subassembly, Stacked subassembly, Random control and Ordered control) versus rest showed activity in a largely overlapping network including: the cuneus (BA 17,19), lingual gyrus (BA 18), middle occipital gyrus (BA 19), the superior parietal lobule and precuneus (BA 7), the inferior parietal lobule (BA 40), the middle frontal gyrus (BA 6), the ventral premotor cortex (BA 6) and the posterior IFG (BA 44).

Table 1
Brain regions activated in the seriated pot condition compared with Rest

Region		Z value	X	Y	Z	BA
Inferior frontal gyrus	L	3.24	−46	4	22	44
Inferior frontal gyrus	R	3.41	56	10	28	44
Middle frontal gyrus	L	4.72	−26	−4	52	6
Precentral gyrus	L	4.13	−46	−2	54	6
Precentral gyrus	R	3.92	52	2	38	6
Postcentral gyrus	L	5.48	−36	−48	60	2
Postcentral gyrus	R	3.31	58	−20	34	2
Inferior parietal lobule	R	4.30	52	−30	48	40
Superior parietal lobule	L	4.51	−24	−56	68	7
Superior parietal lobule	R	5.21	22	−62	64	7
Precuneus	L	4.16	−8	−56	64	7
Inferior temporal gyrus	R	4.94	54	−68	−2	19
Middle occipital gyrus	L	6.05	−42	−70	6	19
Middle occipital gyrus	R	4.85	42	−72	4	19
Inferior occipital gyrus	L	4.69	−40	−84	−10	19
Lingual gyrus	L	4.96	−18	−86	−10	18
Lingual gyrus	R	5.66	6	−80	−10	18
Cuneus	L	4.69	−8	−98	2	17
Cuneus	R	4.70	12	−92	4	17

performed using the correct strategy, but mixing up the order of elements, it was considered a valid trial. We adopted this criterion because we were interested in the time it took to reconstruct the structures according to the different strategies, not necessarily the particular order of element combinations within the strategy. There were five errors in total across the 12 subjects.

Qualitative impressions

Subjects reported that they found the reconstruction of the stacked hierarchical condition most difficult, due to difficulty with manipulating the objects. Subjects found it particularly challenging to balance larger objects on smaller objects. As a result, they had to

Table 2
Brain regions activated in the Seriated subassembly condition compared with Rest

Region		Z value	X	Y	Z	BA
Inferior frontal gyrus	R	3.74	52	12	28	44/9
Middle frontal gyrus	L	4.93	−28	−4	54	6
Middle frontal gyrus	R	4.19	28	0	58	6
Precentral gyrus	L	3.88	−60	6	38	6
Inferior parietal lobule	L	5.00	−44	−42	50	40
Inferior parietal lobule	R	5.04	42	−32	44	40
Superior parietal lobule	L	4.80	−32	−50	54	7
Superior parietal lobule	R	5.09	22	−62	64	7
Precuneus	L	5.62	−22	−64	50	7
Precuneus	R	4.37	26	−66	36	7
Inferior temporal gyrus	R	4.82	54	−68	−2	19
Middle occipital gyrus	L	5.68	−46	−72	4	19
Middle occipital gyrus	R	5.19	42	−72	2	37
Inferior occipital gyrus	L	5.03	−44	−88	−6	18
Fusiform gyrus	R	5.40	28	−78	−12	19
Lingual gyrus	L	4.76	−16	−86	−12	18
Lingual gyrus	R	6.29	6	−80	−10	18
Cuneus	L	5.23	−8	−98	2	17
Cuneus	R	4.88	24	−86	32	19

Table 3
Brain regions activated in the Stacked subassembly condition compared with Rest

Region		Z value	X	Y	Z	BA
Inferior frontal gyrus	R	4.04	54	14	28	44/9
Middle frontal gyrus	L	4.86	−22	−8	50	6
Middle frontal gyrus	R	4.00	64	12	34	9
Superior frontal gyrus	L	4.51	−24	−4	74	6
Precentral gyrus	L	5.10	−36	−50	62	4
Precentral gyrus	L	4.18	−52	−4	38	6
Precentral gyrus	R	4.11	32	−8	54	6
Inferior parietal lobule	L	5.11	−46	−40	52	40
Inferior parietal lobule	R	5.69	46	−32	44	40
Superior parietal lobule	R	4.95	22	−62	64	7
Precuneus	L	5.26	−18	−72	40	77
Inferior temporal gyrus	R	4.95	42	−72	2	37/19
Middle temporal gyrus	R	4.79	56	−62	2	37
Middle occipital gyrus	L	5.72	−42	−70	6	19
Lingual gyrus	L	4.93	−16	−86	−12	18
Lingual gyrus	R	5.33	6	−80	−10	18
Cuneus	L	4.77	−6	−98	4	18
Cuneus	R	5.04	24	−86	34	19

pay more attention to how carefully they grasped and placed each object. They also reported that the random control condition was also difficult, as subjects tried to remember the random sequence of movements, although they were not explicitly asked to do so. Conversely, the seriated pot condition was found to be the easiest to recreate. Subjects had the impression that they used color more than size to help them recreate the sequences, but they said they often relied on both.

Neuroimaging results

Activations common to all action sequences

The stimuli used in this study all show object-directed sequential hand actions. All the observed action sequences activate a fronto-parietal network, previously described as the human mirror neuron system, as well as higher order visual areas, as shown in Fig. 2 and Tables 1–5.

Table 4
Brain regions activated in the Random control condition compared with Rest

Region		Z value	X	Y	Z	BA
Inferior frontal gyrus	R	3.97	56	10	32	44
Middle frontal gyrus	L	5.47	−26	−6	52	6
Middle frontal gyrus	R	3.50	46	4	48	6
Precentral gyrus	L	3.74	−52	2	28	6
Precentral gyrus	R	4.22	32	−6	54	6
Postcentral gyrus	R	4.13	58	−26	42	1
Inferior parietal lobule	L	4.37	−48	−44	54	40
Inferior parietal lobule	R	5.03	34	−48	54	40
Superior parietal lobule	L	5.46	−20	−60	54	7
Superior parietal lobule	R	5.22	22	−62	64	7
Precuneus	R	5.41	24	−76	42	7
Middle temporal gyrus	R	4.88	52	−62	6	37
Middle occipital gyrus	L	5.57	−42	−70	6	19
Lingual gyrus	L	4.91	−16	−86	−12	18
Lingual gyrus	R	5.52	6	−82	−8	18
Cuneus	L	5.32	−8	−98	2	17

Stacked subassembly condition versus Seriated subassembly condition

These two conditions are developmentally co-temporal, and thus equivalent in terms of hierarchical complexity. However, our behavioral data and subjects' reports indicate that the stacked subassembly condition takes longer to construct than the seriated subassembly condition. Subjects indicated that the stacking is motorically more difficult than seriation, as the stacked condition involves more fine dexterous manipulation than the seriated condition. This contrast should thus reveal brain responses influenced by the motoric complexity of the observed actions. The results show reliable signal increases in the inferior frontal gyrus, middle frontal gyrus, insula, ventral premotor cortex, inferior temporal gyrus, postcentral gyrus, inferior parietal lobule and the lingual gyrus. Notably, there was also a reliable signal difference in the supplementary motor area (SMA). However, given that this area was not active against rest in any condition (see Fig. 2), this difference is driven by signal decreases during the seriated subassembly condition (Table 6, Fig. 3).

Stacked subassembly condition versus Seriated pot condition

The stacked subassembly condition is developmentally more complex than the seriated pot condition, because subassembly is a hierarchically more complex strategy than pot. Furthermore, as the behavioral data indicate, the stacked condition is also motorically more complex than the seriated condition. Thus, signal changes revealed by this contrast reflect a difference of both hierarchical and motoric complexity between the subassembly strategy and the pot strategy. Reliable signal increases were found in the middle frontal gyrus, inferior parietal lobule, postcentral gyrus, superior parietal lobule, precuneus and the middle occipital gyrus (Table 6, Fig. 3).

Other contrasts

Contrasts of the seriated subassembly condition versus the seriated pot condition should reveal signal increases related to hierarchical complexity. Neither this, nor the reverse contrast showed reliable signal differences. However, subthreshold signal increases were observed in the inferior parietal cortex for the

Table 5

Brain regions activated in the Ordered control condition compared with Rest

Region		Z value	X	Y	Z	BA
Middle frontal gyrus	L	5.18	−28	−4	54	6
Middle frontal gyrus	R	4.86	24	0	58	6
Precentral gyrus	L	4.18	−54	4	38	6
Precentral gyrus	R	4.17	54	4	38	6
Postcentral gyrus	L	4.43	−56	−24	38	1
Postcentral gyrus	R	3.83	62	−20	36	1
Inferior parietal lobule	L	5.35	−34	−50	56	40
Inferior parietal lobule	R	4.75	44	−32	44	40
Superior parietal lobule	R	5.61	30	−54	62	7
Superior parietal lobule	L	5.69	−20	−60	54	7
Precuneus	R	5.22	24	−76	42	7
Middle temporal gyrus	R	5.04	52	−62	6	37
Middle occipital gyrus	L	6.00	−44	−72	4	37
Superior occipital gyrus	R	4.70	32	−78	24	19
Fusiform gyrus	R	5.39	30	−80	−12	19
Lingual gyrus	L	4.70	−16	−86	−12	18
Lingual gyrus	R	5.61	12	−80	−10	18
Cuneus	L	5.15	−6	−98	4	18

Table 6

Regions significantly more active in the Stacked subassembly condition compared with other experimental conditions

Region		Z value	X	Y	Z	BA
<i>Stacked subassembly vs. seriated subassembly</i>						
Inferior frontal gyrus	L	3.31	−54	6	10	6/44
Inferior frontal gyrus	R	3.24	56	14	28	9
Middle frontal gyrus	L	3.32	−22	−8	56	6
Middle frontal gyrus	R	3.34	28	−6	46	6
Insula	L	3.50	−38	2	14	13
Insula	R	3.54	44	2	12	13
Precentral gyrus	R	2.98	44	−4	38	6
Cingulate gyrus/SMA	L	3.45	−14	2	36	24
Medial frontal gyrus/SMA	R	4.03	10	2	50	6
Postcentral gyrus	L	3.93	−64	−20	32	2
Postcentral gyrus	R	4.02	66	−20	36	2
Inferior parietal lobule	L	2.99	−28	−40	54	40
Inferior parietal lobule	L	3.95	−46	−34	52	40
Inferior parietal lobule	R	3.79	52	−32	52	40
Middle temporal gyrus	R	3.53	54	−54	−8	37
Lingual gyrus	R	3.35	24	−76	−4	18

Stacked subassembly vs. seriated pot

Middle frontal gyrus	L	4.00	−20	0	50	6
Middle frontal gyrus	R	3.67	36	−4	62	6
Postcentral gyrus	L	3.83	−62	−20	32	2
Inferior parietal lobule	L	3.96	−48	−38	54	40
Inferior parietal lobule	R	4.01	52	−32	50	40
Superior parietal lobule	L	3.62	−16	−58	66	7
Superior parietal lobule	R	3.49	32	−52	70	7
Superior parietal lobule	R	3.40	16	−50	62	7
Precuneus	L	2.97	−14	−78	48	7
Fusiform gyrus	L	3.50	−36	−60	−12	37

seriated subassembly condition compared to the developmentally earlier seriated pot condition.

Contrasts of seriated pot and seriated subassembly condition versus either control condition also showed no reliable signal changes, but only weak subthreshold signal increases for the experimental conditions.

Laterality of activations

Based on recent work in our laboratory showing robust bilateral activity in the human mirror neuron system during action observation and imitation (Molnar-Szakacs et al., 2005), it is not surprising that we found a bilateral recruitment of the fronto-parietal networks during observation of hierarchically organized action sequences in this study. As clearly visible in Fig. 2, signal increases in the fronto-parietal mirror neuron system are strikingly bilateral for all conditions. Thus, it appears that in the motor system, hierarchically organized, object-directed action sequences are processed in bilateral networks.

Discussion

We used fMRI to investigate the role of the fronto-parietal human mirror neuron system in representing hierarchical complexity during the observation of object-directed action sequences. We also conducted a behavioral experiment to provide complementary evidence to the neuroimaging findings on the execution component of the observation task used in the fMRI. In both experiments, we presented manual action sequences of varying complexity, adapted

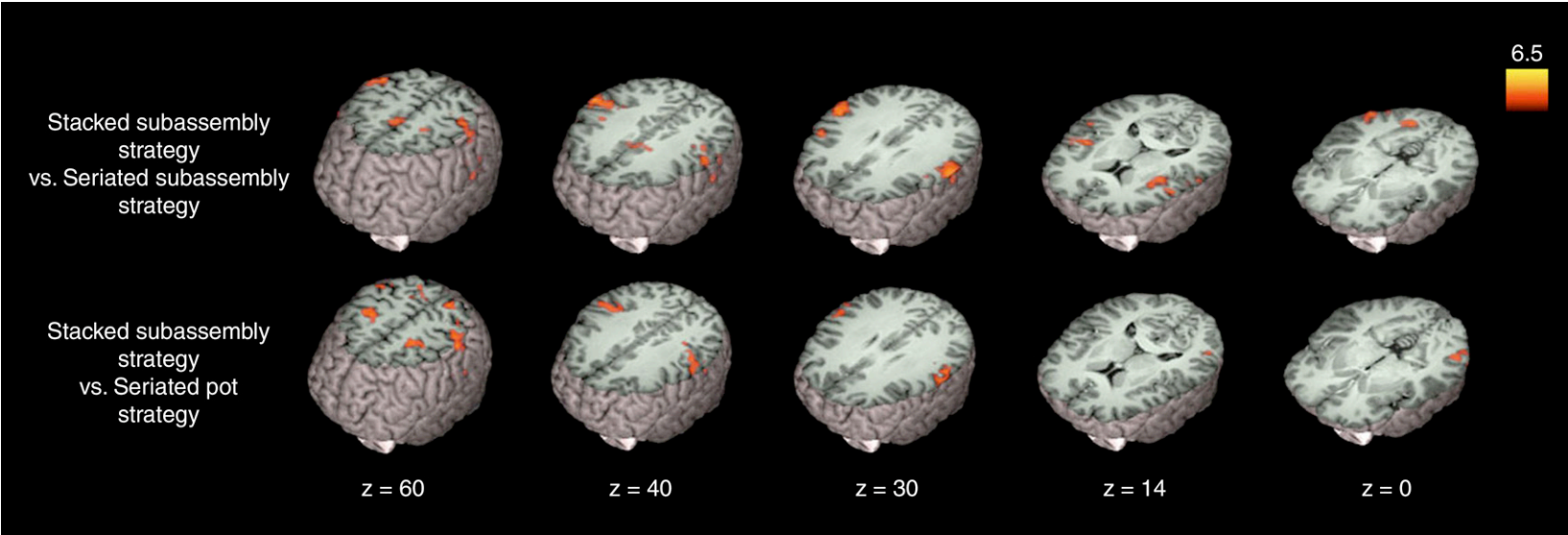


Fig. 3. Contrast of the stacked subassembly condition versus the other experimental conditions revealed activity in regions associated with action representation and also occipito-parietal visual areas. Recruitment of the posterior parietal cortex was consistent in both contrasts, suggesting that this region may be involved in processing unique features of the stacked subassembly condition, such as its motoric complexity.

from children's developmental strategies for hierarchically organized object combination (Greenfield et al., 1972).

The behavioral data reflect the ontogeny of the action strategies in that the hierarchically more complex, and developmentally later subassembly sequences take significantly longer to complete than the hierarchically simpler and developmentally earlier pot sequences. Interestingly, although the stacked and seriated subassembly sequences are developmentally cotemporal, subjects took significantly longer to construct the stacked subassembly condition than the seriated subassembly condition. In qualitative observation, subjects described the stacking as a more difficult manipulation than the seriation, indicating that the stacked sequences are motorically more complex than the seriated sequences. Thus, it appears that the differences among conditions in the behavioral results partly reflect the motoric complexity and dexterous manipulation required of the stacked condition in addition to effects of the different cognitive strategies used to manipulate objects.

The neuroimaging results show that observation of object manipulation sequences independent of complexity recruited classical mirror neuron regions in the posterior inferior frontal gyrus, adjacent premotor cortex and the inferior parietal lobule. The finding that ventral premotor regions including the posterior IFG and inferior parietal regions are activated during the observation of object-directed actions is consistent with findings reported in monkeys (Gallese et al., 1996; Rizzolatti and Fadiga, 1998; Rizzolatti et al., 2000; Rizzolatti and Craighero, 2004; Fogassi et al., 2005). In humans, several previous studies have also shown that the fronto-parietal mirror neuron system is recruited

during observation of object-directed actions (Grafton et al., 1996; Rizzolatti et al., 1996b; Buccino et al., 2001, 2004; Perani et al., 2001; Johnson-Frey et al., 2003; Manthey et al., 2003; Iacoboni et al., 2005).

To look for the effect of coding hierarchical complexity in the mirror neuron system, we contrasted the hierarchically more complex stacked subassembly sequence with the developmentally earlier, and thus hierarchically less complex seriated pot sequence. This contrast revealed increased signal in fronto-parietal areas, in particular in the inferior parietal lobule. However, the contrast of the stacked subassembly condition versus the seriated subassembly condition also showed significant activity in this region. These two latter conditions share hierarchical complexity and are developmentally contemporary. Thus, from these two contrasts, we can conclude that the additional activity elicited by observation of the stacked subassembly condition is not likely related to the developmental progression of hierarchical action structures. This is after all not entirely surprising, given that our subjects are adults and the developmental sequences we used emerge in the first 3 years of life.

During recreation of the observed object manipulation sequences, subjects took significantly longer to replicate the stacked subassembly condition than either the seriated pot condition or the seriated subassembly condition. The stacked subassembly condition results in the construction of a non-seriated structure, which appears to make its execution motorically most difficult. This is due to the fact that larger sized acting objects must be balanced on top of smaller passive objects, which often requires careful dexterous manipulation. Indeed, this is what our subjects

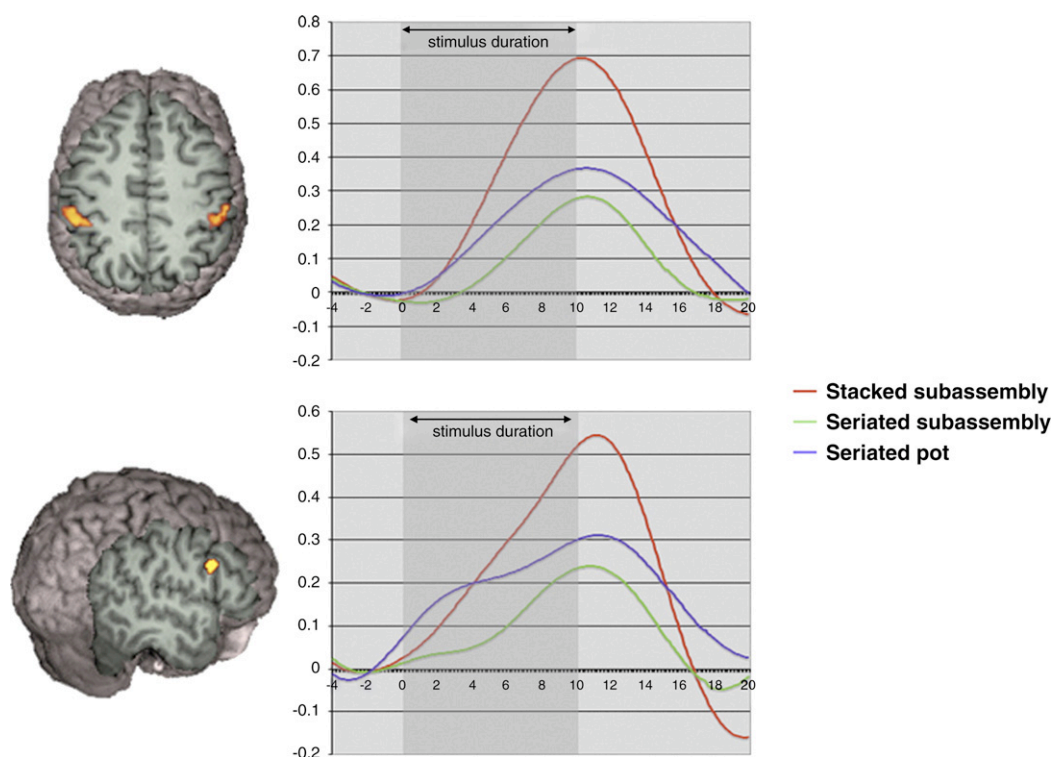


Fig. 4. The time course of BOLD signal change in those voxels of the posterior parietal cortex (top) and the premotor cortex (bottom) that show increased activity in the stacked subassembly condition versus the other experimental conditions. MRI signal in an epoch surrounding each event was averaged to create time courses that show the average signal change in response to an event of each type. Data are expressed as a percent change from baseline. A cubic spline function was used to interpolate data to a 0.1-s resolution, and baseline was calculated as the average value in the 4 s before stimulus onset.

reported in the behavioral experiment. Thus, it appears that the fronto-parietal mirror neuron system represents also the motoric complexity of observed actions, providing a fairly accurate simulation process of the actions of other people. Taken together, the fMRI data and behavioral results seem to suggest that in addition to the cognitive hierarchical complexity, there is a level of motoric complexity in the stacked condition not found in the other conditions leading to an increase in BOLD signal throughout the fronto-parietal network during observation and increased reaction time during construction in adult subjects.

Activation of the fronto-parietal mirror neuron system during mere action observation has been proposed to be the mechanism of action understanding (Rizzolatti and Craighero, 2004). Visual descriptions of observed actions are fed into the fronto-parietal network, leading to activation of the corresponding motor representations. Activation of the fronto-parietal network during observation of object manipulation has also been described as a component of imitation learning (Buccino et al., 2004). To further investigate the role of the fronto-parietal network for action representation in coding motoric complexity during the observation of object manipulation sequences, we looked at the BOLD signal change in the voxels of the premotor and parietal regions that were more active in the stacked subassembly condition versus the other conditions, as shown in Fig. 4. This analysis clearly shows that voxels of both the premotor and posterior parietal cortex are more active during the stacked subassembly condition than during observation of the other two hierarchical sequences.

The pars opercularis and the adjacent ventral premotor cortex have been proposed to code motor schemas relevant for grasping objects (Jeannerod et al., 1995; Rizzolatti et al., 1996b, 2002). This

region also has complementary cognitive functions, which allow it to represent and understand observed actions (Rizzolatti et al., 2002; Rizzolatti and Craighero, 2004). During object manipulation, the premotor regions work in concert with posterior parietal regions (Jeannerod et al., 1995). The essential role of the posterior parietal cortex involves providing descriptions of object characteristics for localization, grasping and action (Jeannerod, 1994; Jeannerod et al., 1995). The posterior parietal lobe is also involved during object manipulation (Filippi et al., 2004), grip-force adjustment during dexterous manipulation (Kuhtz-Buschbeck et al., 2001; Ehrsson et al., 2003) and when using a precision grip versus power grip (Ehrsson et al., 2000). Activity within the fronto-parietal network in the current study likely reflects these functions, as observing the manipulation sequences in our experiment involves an analysis of the seriated cups and stacking rings as well as the grasping movements made towards these objects. Furthermore, our results show that activity within this network appears to be modulated by the perceived motoric complexity of the action.

In a recent study, we found that the human mirror neuron system is involved in interpreting the intentions behind others' actions based on the context within which the action occurs. This process appears to be automatic or unlikely to be modulated by top-down influences, indicating that the mirror neuron system strongly responds to the observation of intentional actions (Iacoboni et al., 2005). Thus, the ability of the mirror neuron system to automatically represent the intention of observed actions may also partly explain the current results. Indeed some of the activity we observe in the inferior frontal cortex may reflect activity related to action and intention representation, however the

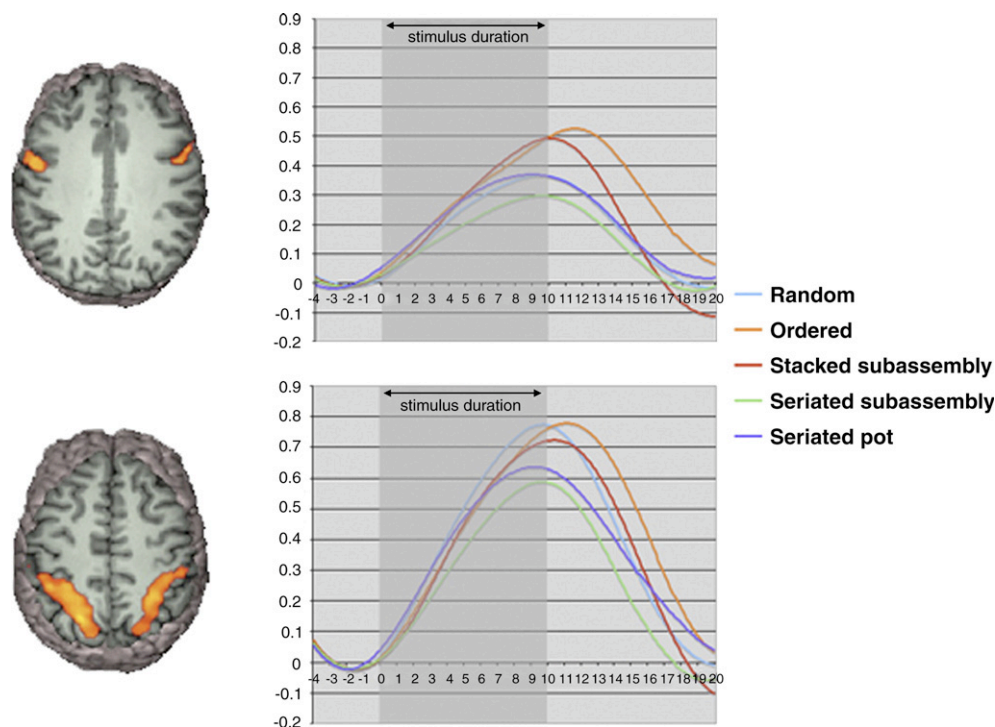


Fig. 5. The time course of BOLD signal changes in the posterior inferior frontal gyrus (top) and in the posterior parietal cortex (bottom) showing remarkably similar activation of fronto-parietal regions for all five conditions. MRI signal in an epoch surrounding each event was averaged to create time courses that show the average signal change in response to an event of each type. Data are expressed as a percent change from baseline. A cubic spline function was used to interpolate data to a 0.1-s resolution, and baseline was calculated as the average value in the 4 s before stimulus onset.

current experimental design does not allow us to directly test hypotheses related to intention understanding. Taken together, these data provide evidence that the fronto-parietal human mirror neuron system mirrors specific motoric aspects of the observed actions, as we originally proposed (Iacoboni et al., 1999).

Recent neuroimaging studies have suggested that the left posterior IFG subserves the general ability to perform sequential operations in both the linguistic and motor modality (Gelfand and Bookheimer, 2003; Bornkessel et al., 2005). Greenfield (1991) had also predicted that the neural processes underlying hierarchically organized sequential object combinations and grammatical combinations are subserved by Broca's area, and are thus lateralized to the left hemisphere. While we did indeed find that observation of object manipulation sequences recruited inferior frontal regions that form part of Broca's area, we found bilateral, rather than just left hemisphere activity in this region. The current finding is in line with recent work in our laboratory showing bilateral activity in the human mirror neuron system during action observation and imitation (Molnar-Szakacs et al., 2005; Aziz-Zadeh et al., 2006).

Neuroimaging studies show that regions of the action recognition network are also important for a variety of language functions (Fadiga et al., 2005; Iacoboni et al., in press). An overlap of activations was found in these regions for action recognition and language production (Hamzei et al., 2003). It was also shown that a fronto-parietal network is engaged during comprehension of hierarchically organized language (Bornkessel et al., 2005). Kimura and colleagues proposed that sequential operations involved in both language and action may explain the co-occurrence of motor and speech deficits in apraxia (Kimura and Archibald, 1974; Lomas and Kimura, 1976). In line with these findings, our current results show that the sequential manipulation of objects recruits the fronto-parietal mirror neuron network for action representation. This finding lends additional support to recent theories proposing that language evolved from the motor system and the two cognitive functions are still governed by the same fundamental rules (Rizzolatti and Arbib, 1998; Arbib, 2005; Greenfield, 2005). Furthermore, our data provide a connection between ontogenetic and neural evidence linking motor and language functions.

This experiment uses a cognitive subtraction approach to explore the brain's responses during observation of action sequences of varying complexity. This method relies on the assumption that the neural processes underlying cognitive functions combine in an independent and additive manner, but this may not be an accurate assumption about brain function (Friston et al., 1996). Our findings have methodological implications for experimental designs adopting subtraction techniques. The use of control conditions that require similar cognitive processing to the conditions of interest in absence of a resting baseline will likely subtract out important neural activity from the experimental conditions, as seems to be the case in our study (see Fig. 5). Future studies that may be interested in exploring questions related to the current one, should consider parametric or factorial designs.

In conclusion, our findings suggest that while the mirror neuron system represents sequences of varying hierarchical complexity, it is not extremely sensitive to the level of hierarchical complexity we have investigated here, given that we found predicted differences between serialised subassembly and pot activation at only a subthreshold level. This is perhaps due to the fact that while our subjects were adults, our stimuli were derived from developmental strategies where the most complex stage is achieved at age 3.

Future studies should investigate the current hypothesis using more complex action sequences. We present behavioral and neuroimaging evidence to suggest that the mirror neuron system codes the motoric complexity of observed action sequences. The ability of the human mirror neuron system to represent action sequences of varying hierarchical complexity may have been foundational in the ability of this neural network to support language evolution.

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