Closely overlapping responses to tools and hands in left lateral occipitotemporal cortex

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Bracci S, Cavina-Pratesi C, Ietswaart M, Caramazza A, Peelen MV. Closely overlapping responses to tools and hands in left lateral occipitotemporal cortex. J Neurophysiol 107: 1443–1456, 2012. First published November 30, 2011; doi:10.1152/jn.00619.2011.—The perception of object-directed actions performed by either hands or tools recruits regions in left fronto-parietal cortex. Here, using functional MRI (fMRI), we tested whether the common role of hands and tools in object manipulation is also reflected in the distribution of response patterns to these categories in visual cortex. In two experiments we found that static pictures of hands and tools activated closely overlapping regions in left lateral occipitotemporal cortex (LOTC). Left LOTC responses to tools selectively overlapped with responses to hands but not with responses to whole bodies, nonhand body parts, other objects, or visual motion. Multivoxel pattern analysis in left LOTC indicated a high degree of similarity between response patterns to hands and tools but not between hands or tools and other body parts. Finally, functional connectivity analysis showed that the left LOTC hand/tool region was selectively connected, relative to neighboring body-, motion-, and object-responsive regions, with regions in left intraparietal sulcus and left premotor cortex that have previously been implicated in hand/tool action-related processing. Taken together, these results suggest that action-related object properties shared by hands and tools are reflected in the organization of high-order visual cortex. We propose that the functional organization of high-order visual cortex partly reflects the organization of downstream functional networks, such as the fronto-parietal action network, due to differences within visual cortex in the connectivity to these networks.

action perception; functional connectivity; visual cortex; ventral stream

THE FUNCTIONAL ORGANIZATION of human occipitotemporal cortex (OTC) partly follows semantic dimensions, including a broad animate-inanimate organization of the ventral stream (Chao et al. 1999), left-lateralized processing of words (Cohen et al. 2000), and right-lateralized processing of socially relevant stimuli such as faces and bodies (Downing et al. 2001; Kanwisher et al. 1997; Peelen and Downing 2005). This organization has been replicated in many studies using various techniques and is highly consistent across individuals. One debate focuses on the functional relevance of domain-specific regions (e.g., the fusiform face area) in the processing of objects from nonpreferred domains (Haxby et al. 2001; Spiridon and Kanwisher 2002). Another question, addressed here, concerns the principles that shape the widely reported functional organization of OTC.

One account of the functional organization of OTC suggests that the segregation of central versus peripheral visual field representations in early visual cortex extends into OTC (Hasson et al. 2002; Levy et al. 2001). This account can explain why objects requiring foveation to be discriminated (e.g., faces or words) are processed in ventral-lateral OTC and objects that are perceived in the periphery (e.g., buildings) preferentially activate ventral-medial OTC. Other accounts highlight the influence of visual shape similarity, describing an overlap between the representations of objects that share form features, such as animals (Haxby et al. 2000), or between unfamiliar objects that are perceived to be similar in shape (Op de Beeck et al. 2008). While these accounts explain part of the functional organization of OTC, they leave several findings unaddressed. For example, they do not explain the lateralization of OTC functions, such as the preferred response to letter strings in the left (but not right) fusiform gyrus (Dehaene et al. 2005; Gaillard et al. 2006; Martin 2006), or the surprisingly normal category-specific organization of OTC in congenitally blind participants (Amedi et al. 2007; Lacey et al. 2007; Mahon et al. 2009; Pietrini et al. 2004; Reich et al. 2011). These and other results indicate that additional organizing principles influence the functional organization of OTC.

An additional organizing principle relates to functional connectivity patterns between OTC and functionally specialized downstream networks (Mahon and Caramazza 2009, 2011; Peelen and Caramazza 2010). This principle posits that objects that are relevant for a specific downstream network are processed in the part of OTC that is best connected to this network. The “functional connectivity constraint principle” may account for the consistent left lateralization of OTC regions selective to letter strings, by taking into consideration the connection these regions must have to left-lateralized language networks (Dehaene et al. 2005; Gaillard et al. 2006; Martin 2006). Similarly, the overlap between face and body responses in right fusiform gyrus (Peelen and Downing 2005) may reflect the need to connect face and body representations to corresponding downstream networks that process social and affective dimensions. Finally, Mahon and colleagues (2007) suggested that tool processing in left medial fusiform gyrus might reflect motor-relevant properties computed in dorsal stream structures. These results suggest that the organization of high-order visual cortex may partly reflect the organization and computations of downstream networks.
Interestingly, there is some (indirect) evidence for a possible overlap between responses to hands and tools in OTC. In a recent study (Bracci et al. 2010), we found that pictures of hands selectively activate an area in left lateral OTC (LOTC) that may fall close to regions previously reported to respond selectively to tools (Chao et al. 1999; Valyear et al. 2007). Execution and perception of object-directed actions involving either a hand or a tool have been found to be processed in corresponding fronto-parietal networks (Jacobs et al. 2010; Lewis 2006; Peeters et al. 2009; Umilta et al. 2008), consistent with the idea that the organization of high-order visual cortex partly reflects the organization of downstream networks, in this case the fronto-parietal action network.

In the present study, we systematically investigated the degree to which functional MRI (fMRI) responses to hands and tools overlap in LOTC. In two studies, we compared the distribution of LOTC responses to hands and tools and measured the functional connectivity between hand- and tool-responsive LOTC regions and downstream functional networks.

In study 1, 14 subjects were tested on three blocked-design experiments. The main experiment was aimed at comparing LOTC responses to hands and tools, relative to animals (see Fig. 1A for example stimuli). The choice of animals as control category was motivated by previous studies on tool perception (Chao et al. 1999; Valyear et al. 2007). The two other experiments were used to localize motion-responsive (moving vs. static dots) and object-responsive (intact vs. scrambled objects) regions in LOTC, in order to compare the overlap between these regions and the hand- and tool-responsive regions. Tool-, hand-, object-, and motion-responsive regions were localized in each individual subject to compare the location and functional profiles of these regions in detail. Finally, a functional connectivity analysis was performed to assess the connectivity of these regions with the rest of the brain.

In study 2 we investigated whether the overlap between tool- and hand-responsive regions in left LOTC is specific to hands or generalizes to other body parts and/or whole bodies. Furthermore, chairs were included as a new control category to replicate and extend the results of study 1 (which used animals as control category). Fourteen new subjects were tested on a blocked-design experiment that included hands, tools, whole bodies, body parts, and chairs (see Fig. 1B for example stimuli). The inclusion of whole bodies and body parts in this experiment allowed for a direct comparison of similarity between tool and hand responses and tool and body responses. Finally, a functional connectivity analysis was performed to test for differences in the connectivity patterns of hand/tool regions and neighboring whole body/body part regions.

MATERIALS AND METHODS

Participants

A total of 30 naïve volunteers were recruited and gave informed consent to take part in one of the studies. Study 1 (n = 15) was approved by the ethics committee of the University of Trento. Study 2 (n = 15) was approved by the ethics committees of the School of Psychology and Sport Sciences of Northumbria University and Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle upon Tyne (Newcastle upon Tyne, UK). All participants were right-handed. Because of excessive head motion two subjects (1 in each study) were excluded from the data analysis.

Experimental Design and Stimuli

Study 1: object category experiment. The object category experiment consisted of two runs lasting 5 min each. The experiment consisted of four conditions: tools, animals, hands, and outdoor scenes. Stimuli were presented centrally, had a size of 12° × 12° (400 × 400 pixels), and consisted of isolated objects on a white background (see Fig. 1A for examples). One scanning run consisted of 21 blocks of 14 s each. Blocks 1, 6, 11, 16, and 21 were fixation-only baseline epochs. In each of the remaining blocks, 20 different stimuli from one category were presented. These stimuli were randomly selected from a total set of 40 stimuli per category. Each stimulus appeared for 350 ms, followed by a blank screen for 350 ms. Twice during each block, the same picture was presented two times in succession. Participants were required to detect these repetitions and report them with a button press (1-back task). Each participant was tested with two different versions of the experiment that counterbalanced for the order of the blocks. In both versions, assignment of category to block was counterbalanced, so that the mean serial position in the scan of each condition was equated.

Study 1: LO localizer. Subjects performed one run of a standard LO localizer (Malach et al. 1995), lasting 5 min. Stimuli consisted of 20 intact and 20 scrambled objects, which were presented in separate blocks. The block structure and task were identical to the object category experiment.

Fig. 1. Examples of stimuli used in the object category experiments. A: study 1: hands, animals, tools, scenes. B: study 2: whole bodies, body parts, hands, tools, chairs.
Study 1: MT/MST localizer. To localize the MT/MST motion complex (Tootell et al. 1995), visual displays of moving and stationary dot patterns were presented either in the left visual field (LVF) or in the right visual field (RVF). In the motion condition, dots shifted from the starting position toward the display’s edge and back toward the fixation (0.5°/s), alternating direction every three frames. In the static condition, the dots remained still. The single MT/MST localizer run lasted 8 min 48 s, during which the four stimulus conditions (static dots in the LVF, moving dots in the LVF, static dots in the RVF, and moving dots in the RVF), each lasting 16 s, were interleaved with fixation blocks (16 s). Each stimulus condition was repeated four times in a random order within the run. Fixation blocks also appeared at the beginning and end of each run. The fixation point alternated in color (red, yellow, green, blue) every 500 ms. To maintain attention, participants were instructed to press a button with their right index finger whenever the central fixation point turned red.

Study 2: object category experiment. The object category experiment consisted of two functional runs lasting 7 min 14 s each. Within each run five stimulus categories (whole bodies without head, body parts, hands, tools, and chairs) were organized into five quasi-random sequences of five stimulus blocks, interleaved with fixation blocks (14 s). Fixation blocks also appeared at the beginning and end of each run. Within each stimulus block, stimuli were centrally presented for 800 ms with a blank interstimulus interval (ISI) of 200 ms. The stimulus set consisted of 75 different grayscale photographs per object category (see Fig. 1B for examples). The stimulus set was different from the stimulus set used in study 1. Each photograph consisted of an isolated object on a white background (400 × 400 pixels). To maintain attention, participants were asked to perform a 1-back repetition detection task (either 1 or 2 repetitions were presented within a block).

Part of the data of study 2 has been used previously to show hand-responsive regions in OTC (Bracci et al. 2010). Here, we present new analyses of these data, investigating the overlap between tool and hand responses.

Spatial Frequency Analysis

To test for differences in the spatial frequency content of the stimuli used in the object category experiments (study 1 and study 2), we compared the power spectra of the images across categories. Each image was Fourier transformed to quantify the spectral power as a function of spatial frequency. Because, for natural images, spectral power varies approximately as 1/fα as a function of spatial frequency, we used α as a measure of the distribution of spectral power across spatial frequency (see, e.g., van der Schaaf and van Hateren 1996). We estimated the 1/f exponent (α) by fitting the 1/f model to the power spectrum of each image. These values were then statistically compared across pairs of categories with independent t-tests. For the stimuli used in study 1, there were no differences between the α of animals (2.04), hands (2.05), and tools (2.05; P > 0.7, for all tests). The α of scenes (1.79) was significantly lower than that of each of the other categories (P < 0.001, for all tests). Thus, for study 1, fMRI differences between hands, tools, and animals are unlikely to be related to differences in spatial frequency content. For study 2, which used a different stimulus set, the α of hands (2.21) and tools (2.22) was significantly higher than the α of chairs (1.96; P < 0.001, for both tests) and whole bodies (2.14; P = 0.046, for both tests) but were both lower than the α for body parts [2.30; P = 0.032 (hands-body parts); P = 0.09 (tools-body parts)]. Thus, although the spatial frequency content of hands and tools in study 2 differed from that of the other conditions, these differences were not in a consistent direction. Furthermore, it should be noted that most of these differences were small, only marginally significant, and would not survive correction for multiple comparisons.

Apparatus and Data Acquisition

Stimulus presentation was controlled by a PC running the Psychophysics Toolbox package (Brainard 1997) in MATLAB (MathWorks, Natick, MA). Pictures were projected onto a screen and were viewed through a mirror mounted on the head coil.

Functional and structural data for study 1 were collected at the Center for Mind/Brain Sciences, University of Trento. All images were acquired on a Bruker BioSpin MedSpec 4-T scanner (Bruker BioSpin, Rheinstetten, Germany). Functional images were acquired with echo planar (EPI) T2*-weighted scans. Acquisition parameters were repetition time (TR) of 2 s, echo time (TE) of 33 ms, flip angle (FA) of 73°, field of view (FoV) of 192 mm, and matrix size of 64 × 64. Each functional acquisition consisted of 34 axial slices (which covered the whole cerebral cortex) with a thickness of 3 mm and a gap of 33% (1 mm). Structural images were acquired with an MP-RAGE sequence, with 1 × 1 × 1-mm resolution.

Functional and structural data for study 2 were collected at the Newcastle Magnetic Resonance Centre, School of Clinical Medical Sciences, University of Newcastle upon Tyne. All images were acquired on a Philips Achieva 3-T scanner with a SENSE eight-channel birdcage head coil. Functional images were acquired with echo planar (EPI) T2*-weighted scans. Acquisition parameters were TR = 2 s, TE = 30 ms, FA = 90°, FoV = 192, and matrix size = 64 × 64. Each functional acquisition consisted of 30 axial slices (which covered the whole cerebral cortex) with a thickness of 4 mm and no gap between slices. Structural images were acquired with an MP-RAGE sequence, with 1 × 1 × 1-mm resolution.

Preprocessing

For both studies, data preprocessing and analysis were performed with Brain Voyager QX (version 2.20; Brain Innovation, Maastricht, The Netherlands). Three-dimensional motion correction was performed to correct for subject’s head motion. After linear trend removal, functional data underwent high-pass temporal filtering (cutoff 3 cycles per time course). For the functional connectivity analysis (but not for the other analyses), functional volumes were spatially smoothed (6-mm full-width half-maximum isotropic Gaussian kernel). Manual coregistration was performed to align the functional images with the T1 anatomical images. Subsequently the anatomical images were transformed into Talairach stereotactic space, and this transformation was applied to the aligned functional data, which was interpolated to 1 × 1 × 1 mm.

Statistical Analysis

For both studies, data were analyzed with the general linear model (GLM; 1 for each experiment). Each GLM included the conditions of interest, as well as the six parameters from the motion correction procedure (x, y, z for translation and for rotation). Predictors’ time courses were modeled with a linear model of hemodynamic response using the default Brain Voyager QX “two-gamma” function. Before computing the GLM, functional runs were z-normalized.

Region of interest definition. The aim of the present study was to provide a detailed investigation of the overlap between fMRI responses to hands and tools in OTC. Exploratory whole-brain conjunction analyses on both data sets indicated that, within OTC, such overlap was only present in left LOTC, in agreement with previous studies showing that left LOTC responds to both tools (Chao et al. 1999; Valyear et al. 2007) and hands (Bracci et al. 2010). The analyses reported in this paper therefore primarily focused on this part of OTC using a region of interest (ROI) approach. Four types of analyses were performed: individual-subject ROI activation analysis, ROI overlap analysis, multivoxel pattern analysis (MVPa), and functional connectivity analysis. Given the different objectives of these analyses, it was not possible (or desirable) to use the same ROI.
definition for each analysis. Thus, where necessary, ROI definition (threshold and/or contrast) differed between analyses. For example, in the individual-subject ROI activation analysis it was important to use a split-half procedure to ensure that the data reported were independent of ROI selection. For the ROI overlap analysis all data could be used for defining ROIs, and the interest was in the degree of overlap between all contiguously activated voxels. For MVPA, it was important to equate the number of voxels across ROIs, given previous research showing that the number of voxels influences this type of analysis (e.g., Eger et al. 2008). Finally, for the functional connectivity analysis, it was desirable to define nonoverlapping ROIs to reveal regionally selective connectivity patterns. These considerations led us to different ROI definitions depending on the type of analysis, as described in more detail below.

**Individual-subject ROI activation analysis.** In both studies, we defined ROIs within the LOTC in both hemispheres, except for tool-responsive regions, which could only be defined in left LOTC (coordinates range: x = −68 < x < −18, −45 < y < −95, −30 < z < 20). ROIs were localized in each individual subject with comparisons of interest. In study 1, ROIs were defined with the following contrasts. 1) Hands and tools were each contrasted with animals in the object category experiment. This contrast was used in previous studies on tool representations (Chao et al. 1999; Valyear et al. 2007). 2) Intact objects were contrasted with scrambled objects in the LO localizer. 3) Moving objects were contrasted with static dots in the MT/MST localizer. In study 2, ROIs were defined by contrasting each category of interest (hands, tools, bodies, body parts) with chairs (e.g., hands vs. chairs). This contrast was previously used to define hand-selective responses in left LOTC (Bracci et al. 2010). Thresholds were set at P < 0.001 (uncorrected). ROIs were restricted to 10 × 10 × 10-mm cubes centered on the peak voxel of each area within the LOTC region. To avoid circularity, data used for statistical testing were always independent from data used to define ROIs. Thus statistical maps used for defining ROIs were computed using one run (e.g., run 1) and analysis of the percent BOLD signal change (%BSC) was performed on data from the other run (e.g., run 2), and vice versa. %BSC was computed using the peak response by averaging the response of six volumes around the peak activity (volumes 3 to 8 after block onset, taking into account the hemodynamic lag and block duration) relative to a common baseline for all conditions (averaged response for volumes −2 to 9, before block onset). We used %BSC because it reflects the signal magnitude relative to baseline without making any assumptions about the shape of the BOLD response, in contrast to GLM-related beta weights that rely on several such assumptions. The average %BSC data were statistically compared by analysis of variance (ANOVA).

**ROI overlap analysis.** The voxel overlap among functionally defined ROIs in left LOTC was measured for study 2. Unlike the ROI activation analysis, ROIs for the overlap analysis were defined using both functional runs. Given the increase of power relative to the ROI activation analysis (in which ROIs were defined using 1 functional run), the threshold was set to P < 0.05 (Bonferroni corrected) for the contrasts of interest (e.g., hands vs. chairs; see RESULTS). Because we were interested in the full extent of overlap between ROIs, all contiguously activated voxels were included. An overlap index was calculated by dividing the number of voxels common to two ROIs (e.g., ROIhand ∩ ROItool) by the number of voxels of the smaller of the two ROIs. This choice of denominator was preferred over other possible definitions of overlap size because it is less influenced by relative size differences between ROIs. An index of 1 indicates that the smaller of two ROIs falls completely within the other ROI, whereas an index of 0 indicates no overlap between two ROIs.

**Multivoxel pattern analysis.** Correlation-based MVPA (Haxby et al. 2001) was performed for the object category data set of study 2. MVPA was performed in several functionally defined ROIs, localized in each subject individually using both runs of the object category experiment. The aim of this analysis was to reveal the similarity of response patterns to the different object categories within an LOTC region selective for hands, bodies, body parts, and tools (relative to chairs). This analysis followed the approach of earlier work that similarly aimed to establish the similarity of responses to different categories within OTC (Downing et al. 2007; Peelen et al. 2006).

The main ROI, “LOTC-cat,” was defined by contrasting the average response to whole bodies, body parts, hands, and tools with the response to chairs (the acronym “cat” refers to categories of interest). Two additional functionally defined regions, one in left fusiform gyrus (“FG-cat”) and one in left occipital cortex (“OC-all”), were also included as control regions. FG-cat served as a high-level control region, located in high-order visual cortex, which could be defined by the same contrast as used for LOTC-cat, owing to its selectivity to bodies, body parts, and tools, as reported in previous studies (Chao et al. 1999; Peelen and Downing 2007). OC-all served as a low-level control region, located posterior to LOTC-cat and defined by contrasting the average response to all stimulus blocks (hands, tools, bodies, body parts, chairs) with fixation baseline (“all” refers to all stimulus categories). The threshold for LOTC-cat and OC-all was set to P < 0.0001 (uncorrected), while the threshold for FG-cat was set to P < 0.01 (uncorrected). These thresholds were chosen to approximately equate the number of voxels included in each ROI, which may influence the results of MVPA (see, e.g., Eger et al. 2008). For the same reason, all ROIs were restricted to cubes of 2-cm width centered on the activation peak. Within these ROIs, t values were extracted for each voxel, each condition, and each run. For each voxel, the average t value was normalized to a mean of zero by subtracting the mean t value across all conditions from the t value of each condition, separately for each run (Haxby et al. 2001). Voxelwise correlations were then computed comparing the activity patterns in run 1 with those in run 2. The chairs condition was not included since it was used as control condition in the definition of LOTC-cat and FG-cat. This analysis thus resulted in a 4 × 4 correlation matrix for each subject and ROI, providing an estimate of the neural similarity of the four object categories. Correlations were Fisher transformed \( \frac{0.5 \times \log((1 + r)/(1 - r))}{10.220.3} \) and tested with pairwise t-tests with subject as random factor. It should be noted that the response normalization eliminates the influence of differences in the mean response level between voxels and emphasizes between-condition differences in response patterns. As a consequence, the correlation values should be viewed only as relative distance measures between the response patterns evoked by the conditions of the experiment. An absolute correlation value between two conditions is not interpretable, since this value directly depends on the similarity between all other conditions included in the analysis.

**Functional connectivity analysis.** Functional connectivity analysis for the hand/tool region in left LOTC was performed for both studies. In study 1, the hand/tool region was localized in each individual subject by taking the conjunction of the contrasts hands vs. animals and tools vs. animals. Two additional regions were also included: left LO (intact vs. scrambled objects) and left MT/MST (moving vs. static dots). In study 2, the hand/tool region was localized in each individual subject by taking the conjunction of the contrasts hands vs. whole body and body parts and tools vs. chairs. An additional body-responsive region was localized by contrasting whole body and body parts vs. hands. All seed regions were defined by taking significant (P < 0.001, uncorrected) voxels within a 10 × 10 × 10-mm cube centered on the peak voxel of each ROI. The similarity of responses to different cat:ies in this way was to separate, as much as possible, regions that were selectively activated by hands and tools (main seed region) versus bodies and body parts (control seed region), in order to reveal selective functional connectivity to each region. Granger causality maps (GCM) were computed separately for each subject and each seed ROI with Brain Voyager Granger Causality Mapping Plug-In (Roebroeck et al. 2005). This method allows for computing directed and instantaneous influences between the seed region and every other voxel in the brain.
the brain. Because interactions between brain regions are expected to occur at a time scale well below the sampling rate (TR) of 2 s, most of the directed (causal) influences (e.g., a causal influence from the seed region to another region) will be captured in the instantaneous influence term (Roebroeck et al. 2005). This instantaneous influence quantifies the improvement in the prediction of the current BOLD value of one region (e.g., the seed region) by including the current BOLD value of another region (e.g., the target region) in a linear model already containing the past BOLD values of both regions (Roebroeck et al. 2005). This is similar to a partial correlation between time courses. An instantaneous influence map for each reference region was computed using all functional volumes of the preprocessed data of the two concatenated functional runs (6-mm smoothed). Direct contrasts of the resulting functional connectivity maps were computed by using group-average paired-sample \( t \)-tests to reveal voxels that were significantly more functionally connected to the main seed region (hand/tool regions) relative to various control regions (left LO and left MT/MST in study 1 and left body-responsive region in study 2). The threshold was set to \( P < 0.005 \) (uncorrected), with a minimum cluster size of 1,000 mm\(^3\).

**RESULTS**

**Study 1**

**Individual-subject ROI activation analysis.** All 14 participants showed significant responses to hands and tools, each relative to animals, in left LOTC, indicating that these responses were highly reliable at the individual-subject level. Importantly, an overlap between hand- and tool-responsive activations in left LOTC was found in all but one participant (Fig. 2). In right LOTC all 14 participants showed activation to hands, while only 5 participants showed activation to tools. Because of the low number of participants, the right LOTC-tool region was not included in the analysis. Object-selective LO and motion-selective MT/MST were also localized in each subject in both hemispheres by comparing pictures of intact objects versus pictures of scrambled objects and moving dots versus static dots, respectively. Mean Talairach coordinates and cluster sizes for all ROIs are reported in Table 1. Subsequently, the %BSC for each condition was extracted in each of these ROIs (Fig. 3A), using independent data sets (using a split-half analysis, see MATERIALS AND METHODS). These responses were tested in a \( 7 \times 4 \) ANOVA with ROI (left LOTC-hand, right LOTC-hand, left LOTC-tool, left LO, right LO, left MT/MST, right MT/MST) and category (tools, animals, scenes, hands) as within-subject factors. Results revealed a significant ROI \( \times \) category interaction \([F(18,234) = 9.67, P < 0.001]\), indicating differences in the functional selectivity profiles of the ROIs (Fig. 3B). Post hoc pairwise \( t \)-tests showed

**Table 1. Talairach coordinates for ROIs in study 1 and study 2**

<table>
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<tr>
<th></th>
<th>Left OTC</th>
<th>Right OTC</th>
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<td></td>
<td>( x )</td>
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<tr>
<td><strong>Study 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOTC-tool</td>
<td>-48</td>
<td>-65</td>
</tr>
<tr>
<td>LOTC-hand</td>
<td>-49</td>
<td>-65</td>
</tr>
<tr>
<td>MT/MST</td>
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<td>-72</td>
</tr>
<tr>
<td>LO</td>
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<td>-76</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td></td>
<td></td>
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<tr>
<td>LOTC-tool</td>
<td>-46</td>
<td>-68</td>
</tr>
<tr>
<td>LOTC-hand</td>
<td>-46</td>
<td>-68</td>
</tr>
<tr>
<td>LOTC-whole body</td>
<td>-46</td>
<td>-73</td>
</tr>
<tr>
<td>LOTC-body part</td>
<td>-47</td>
<td>-73</td>
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Mean Talairach coordinates and cluster size are reported for individual-subject regions of interest (ROIs) localized with the comparison of tools > animals (LOTC-tool), hands > animals (LOTC-hand), intact objects > scrambled objects (LO), and moving dots > static dots (MT/MST) in study 1 and hands > chairs (LOTC-hand), tools > chairs (LOTC-tool), whole bodies > chairs (LOTC-whole body), and body parts > chairs (LOTC-body part) in study 2. ROIs were defined for both functional runs separately. Values are the average values of the ROIs defined in the 2 runs. Threshold \( P < 0.001 \), uncorrected. OTC, occipitotemporal cortex; LOTC, lateral OTC.
significantly stronger responses to hands than to each of the other categories in both left and right LOTC-hand ($P < 0.001$, for all tests). Tools elicited the second highest response in left LOTC-hand ($P < 0.001$, relative to animals and scenes). By contrast, in right LOTC-hand responses to tools and animals did not differ from each other ($P > 0.7$). Similarly, left LOTC-tool showed stronger responses for both hands and tools relative to animals and scenes ($P < 0.001$, for all tests), but there was no difference between tools and hands ($P > 0.5$). There were no differences between tools and hands versus animals in LO and MT/MST in both hemispheres ($P > 0.05$, for all comparisons). See Table 2 for the total number of planned comparisons and corresponding Bonferroni-corrected $P$ values.

Taken together, these analyses show that responses to tools and hands, relative to animals, largely overlap in left LOTC (Fig. 2). Moreover, they show that this overlap is unlikely to be related to a common activation of motion or general object processing regions, since MT/MST and LO did not overlap substantially with tool- or hand-responsive regions and did not respond more to either hands or tools relative to animals. Next, we explored the functional connectivity between the left LOTC region activated by both hands and tools and the rest of the brain, to test whether this region was differentially connected (relative to left MT/MST and left LO) to fronto-parietal regions previously implicated in action observation and execution (e.g., Buccino et al. 2001; Culham et al. 2006; Grafton and Hamilton 2007).

**Functional connectivity analysis.** Analysis of functional connectivity was performed by comparing the whole-brain connectivity of three seed regions (see MATERIALS AND METHODS). The main seed ROI was the left LOTC region commonly activated by both hands and tools (both relative to animals), which could be defined in 13 of 14 subjects (see MATERIALS AND METHODS). Nearby motion- and object-selective regions were also defined in these subjects. Mean cluster size (mm$^3$) and Talairach coordinates ($x,y,z$) of the ROIs were left hand/tool region (389 mm$^3$; $x,y,z = -48, -66, -5$), left MT/MST (378 mm$^3$; $x,y,z = -42, -73, -3$), and left LO (537 mm$^3$; $x,y,z = -41, -78, -9$). Figure 4A, left, shows hand/tool and LO seed regions in three representative subjects. Subsequently, the functional connectivity of these regions was computed for each subject individually, resulting in 13 connectivity maps for each of the 3 regions (Fig. 4A, center). These maps were directly contrasted with each other with group-average paired-sample $t$-tests, in order to test for regionally selective functional connectivity that was consistent across subjects. As shown in Fig. 4A, right, the left hand/tool region was more strongly connected to a region in left anterior intraparietal sulcus [aIPS; $x,y,z = -53, -32, 34$, $t(13) = 5.0$, $P < 0.0005$] than was the object-selective region (LO). This is in agreement with recent structural and functional connectivity studies showing connectivity between left LOTC and left parietal regions (Noppeney et al. 2006; Ramayya et al. 2010; Simmons and Martin 2011; Uddin et al. 2010). Analysis on the %BSC within the aIPS region revealed that responses to hands and tools were signif-

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**Fig. 3.** Regions of interest (ROIs) and mean responses for study 1. A: ROIs in 4 representative subjects: hand responsive (hands > animals, yellow color coded), tool responsive (tools > animals, blue color coded), LO (intact > scrambled objects, green color coded), and MT/MST (moving > static dots, red color coded). See Table 1 for details of the ROIs. B: average activity [% BOLD signal change (%BSC)] for each stimulus category (hands, tools, animals, scenes) extracted from individual-subject ROIs using independent data. LH, left hemisphere; RH, right hemisphere; LOTC, lateral occipitotemporal cortex. Error bars indicate SE.
Table 2. Statistical analysis overview

<table>
<thead>
<tr>
<th>Study</th>
<th>Statistical Analysis</th>
<th>Single Test</th>
<th>No. of Comparisons</th>
<th>t Value</th>
<th>Uncorrected P Value</th>
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<tr>
<td>Study 1</td>
<td>ILOTChand</td>
<td>ROIs %BSC pairwise t-tests</td>
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<td></td>
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<td>All planned comparisons</td>
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<td>0.025</td>
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Overview of statistical analyses in study 1 and study 2 for contrasts of interest that reached significance at P < 0.05 (uncorrected). The number of comparisons for each test is given, together with the corresponding Bonferroni-corrected P values. Also reported are t values and uncorrected P values. Uncorrected P values displayed in bold survived correction for multiple comparisons. %BSC, %BOLD signal change.

significantly higher than responses to animals and scenes (P < 0.001, for both tests). Conversely, left LO (relative to the left hand/tool region) showed significantly stronger functional connectivity with regions in early visual cortex (Fig. 4A, right). A similar direct contrast between the functional connectivity of the hand/tool region and MT/MST did not reveal significant differences at this threshold. However, at a more liberal threshold (P < 0.05, uncorrected), significantly stronger functional connectivity between the hand/tool region (relative to MT/ MST) and a region in left parietal cortex (x,y,z = −39, −57, 47) was also observed.

These functional connectivity results indicate that the LOTC region representing both hands and tools is selectively connected (relative to neighboring regions) to a region in left parietal cortex that has previously been linked to hand/tool action observation and execution (e.g., Bach et al. 2010; Decety et al. 1997; Grafton and Hamilton 2007; Lewis 2006; Valyear et al. 2007).

Study 2

Individual-subject ROI activation analysis. Hand-, tool-, whole body-, and body part-responsive regions were localized in individual subjects by contrasting each category with chairs. All regions could be defined in each individual participant, again highlighting the reliability of these LOTC regions. Talairach coordinates for hand- and tool-responsive regions were similar to those of study 1 (Table 1). The functional response profile of each ROI was investigated by extracting %BSC for each condition, using independent data. These values were tested in a 7 (ROI) × 5 (category) ANOVA with ROI (left LOTC-tool, left LOTC-hand, right LOTC-hand, left LOTC-whole body, right LOTC-whole body, left LOTC-body part, right LOTC-body part) and category (hands, tools, chairs, whole bodies, body parts) as within-subject factors. Results revealed a significant ROI × category interaction [F(24, 312) = 11.39, P < 0.001], indicating differences in the functional selectivity profiles of the ROIs. Follow-up t-tests revealed a selective response to hands in left LOTC-hand (P < 0.001, for all tests). Left LOTC-tool was also selective to hands (P < 0.001, for all tests except hands vs. body parts: P = 0.02). Left LOTC-tool responses were significantly higher to tools than chairs (P < 0.001) but did not differ between tools and whole bodies and body parts (P > 0.05). Figure 5 shows the functional profile of the ROIs.

ROI overlap analysis. To quantify the extent of overlap between the regions, we calculated an overlap index for each pairwise combination of regions. For this analysis, ROIs were defined using both functional runs combined (Fig. 6A; see
A large overlap was found between tool and hand responses (80% overlap; see Fig. 6B), which was significantly larger than the overlap between tools and whole bodies [34%; \( t(13) = 5.73, P < 0.001 \)], tools and body parts [38%; \( t(13) = 5.60, P < 0.001 \)], hands and whole bodies [42%; \( t(13) = 4.39, P < 0.001 \)], and hands and body parts [47%; \( t(13) = 4.03, P < 0.001 \)]. Next, we tested the Euclidean distance between the Talairach coordinates (center of mass) of each of these regions. This analysis revealed that hand- and tool-selective regions were located close to each other (distance = 5.6 mm) and significantly closer than tools and whole bodies [10.6 mm; \( t(13) = 5.53, P < 0.001 \)] and tools and body parts [9.4 mm; \( t(13) = 4.16, P < 0.001 \)]. No significant differences were found between the hand-tool distance and the distance between hands and whole bodies (\( P > 0.10 \)) or hands and body parts (\( P > 0.20 \); see Fig. 6C). See Table 2 for the
total number of planned comparisons and corresponding Bonferroni-corrected $P$ values.

These results provide further evidence for a close and specific correspondence between tool and hand responses in left LOTC, which was reflected in a large degree of overlap of these activations. Furthermore, similar comparisons of tools with whole bodies and nonhand body parts revealed that this correspondence was specific to hands. Indeed, the hand-responsive region overlapped more strongly with the tool-responsive region than with the whole body-responsive and body part-responsive regions, even though hands are themselves body parts and hands were visible in the whole body stimuli.

Multivoxel pattern analysis. Analyses that take into account similarities in multivoxel response patterns have been shown to

Fig. 5. Mean responses in each ROI for conditions of study 2 (hands, tools, chairs, bodies, body parts). Average activity (%BSC) for each stimulus category was extracted from individual-subject ROIs using independent data. Error bars indicate SE.

Fig. 6. Overlap index and Euclidean distance results in study 2. A: ROIs used to perform the overlap index and Euclidean distance calculations are shown in 5 representative subjects. B: overlap index represents the percentage of shared voxels between 2 category-responsive regions (e.g., between hand- and tool-responsive regions, leftmost bar), computed by dividing the number of voxels common to 2 ROIs by the number of voxels of the smaller of the 2 ROIs (see MATERIALS AND METHODS). C: Euclidean distance (in mm) between centers of mass of the ROIs. Error bars indicate SE.
be more sensitive than standard univariate analyses in assessing the similarity of overlapping activations (Peelen et al. 2006). Here, MVPA was employed to measure the similarity of hand, tool, body, and body part responses in several regions of OTC. If, as we hypothesized, the distribution of tool responses within left LOTC is more similar to the distribution of nonhand body part responses than to the distribution of nonhand body part responses, we would expect a higher correlation between the response patterns to tools and hands than between the response patterns to tools and body parts. To test this hypothesis, we performed MVPA in several functionally defined regions. The main ROI was LOTC-cat, defined by contrasting the average response to the four categories of interest (hands, tools, body parts, whole bodies) with the response to chairs. As control regions (see also MATERIALS AND METHODS), we defined a region posterior to LOTC-cat in left occipital cortex (OC-all) and a region ventral and anterior to LOTC-cat in the left fusiform gyrus (FG-cat). Mean cluster size (mm$^3$) and Talairach coordinates ($x$, $y$, $z$) of each ROI were LOTC-cat (3,714 mm$^3$; $x$, $y$, $z$ = −46, −70, 0), FG-cat (2,221 mm$^3$; $x$, $y$, $z$ = −34, −41, −18), and OC-all (4,190 mm$^3$; $x$, $y$, $z$ = −36, −85, −1). Figure 7A shows the three ROIs in a representative subject. Within these ROIs, we then correlated the voxelwise patterns of activity between each of the conditions of interest across the two runs (e.g., hands_run1 - tools_run2). The mean univariate response in the LOTC-cat (Fig. 7B) was highest to hands, whole bodies, and body parts and weakest to tools. These differences were expected based on the response profiles of the separately defined left LOTC regions (Fig. 4). Note that these differences may affect the results of the MVPA, possibly inflating the correlations among hands, whole bodies, and body parts, relative to correlations involving tools. This may work against our hypothesis of a strong correlation between hands and tools, relative to other between-category correlations (e.g., hands and whole bodies).

Averaged across the two runwise comparisons, there was a positive correlation between hands and tools, indicating relatively similar response patterns for hands and tools in LOTC-cat (Fig. 7C). The positive correlation between the tool and hand response patterns was highly specific to tools and hands, with both whole bodies and body parts correlating negatively with tools (tools-whole bodies: $r = 0.57$; tools-body parts: $r = 0.41$) and hands (hands-whole bodies: $r = 0.56$; hands-body parts: $r = 0.45$). Pairwise t-tests on Fisher-
transformed correlations, with subject as random factor, confirmed that the correlation between hands and tools was higher than all other correlations involving hands or tools ($P < 0.001$, for all tests).

A different result was found in the control regions, OC-all and FG-cat (Fig. 7C). Similar to LOTC-cat, these regions showed generally high within-category correlations for all conditions (Fig. 7C). In OC-all there were no significant differences among the between-condition correlations ($P > 0.05$, for all tests). In FG-cat the correlation between body parts and whole bodies was higher than the correlation between hands and tools [$t(13) = 2.95$, $P < 0.01$] and the correlation between hands and tools was higher than the correlation between body parts and hands [$t(13) = 2.53$, $P < 0.05$], although these two tests did not survive correction for multiple comparisons. See Table 2 for the total number of planned comparisons and corresponding Bonferroni-corrected $P$ values.

These results indicate a relatively high degree of similarity between multivoxel response patterns to tools and hands in left LOTC. Furthermore, they show that, by contrast, response patterns to tools and body parts and response patterns to tools and whole bodies are relatively dissimilar to one another. Likewise, response patterns to hands and whole bodies and response patterns to hands and body parts were dissimilar to each other, even though hands are part of the body. Finally, the similarity between hands and tools was specific to left LOTC and was not found in neighboring regions of visual cortex.

**Functional connectivity analysis.** Similar to study 1, a functional connectivity analysis was performed with the seed region being the left LOTC region commonly activated by both hands and tools. For this analysis, the hand/tool overlap region was defined by the conjunction of hands versus whole bodies and body parts and tools versus chairs. A body-responsive region was defined based on the contrast between whole bodies and body parts versus hands. These contrasts were chosen to minimize the overlap between the hand/tool region and the body part region. These regions could be defined in 14 of 14 subjects. Mean cluster size ($\text{mm}^3$) and Talairach coordinates ($x,y,z$) of each ROI were left hand/tool region (421 $\text{mm}^3$; $x,y,z = -46, -68, -1$) and left body region (576 $\text{mm}^3$; $x,y,z = -42, -79, 2$). Fig. 4B, left, shows hand/tool and body seed regions in three representative subjects. The functional connectivity of these regions with every other voxel in the brain was computed for each subject individually. These whole brain connectivity maps were directly contrasted with each other by group-average paired-sample $t$-tests, in order to test for regionally selective functional connectivity that was consistent across subjects. As shown in Fig. 4B, right, the hand/tool region was more strongly connected to regions in left aIPS [$x,y,z = -41, -44, 45$, $t(13) = 4.5$, $P < 0.001$] and left dorsal premotor cortex [dPM; $x,y,z = -37, -15, 52$, $t(13) = 5.6$, $P < 0.0001$] than was the body-responsive region. In both regions, analysis of the %BSC revealed that the responses to hands and tools did not differ from responses to whole bodies, body parts, or chairs ($P > 0.05$, for all tests). There were no regions that showed significantly stronger connectivity with the body region than the hand/tool region.

These results confirm the functional connectivity findings of study 1 and show that the functional connectivity between the left LOTC and regions of a left fronto-parietal network was strongest at the location where hands and tools were represented, relative to the location where nonhand body parts were represented.

**DISCUSSION**

In two independent studies, hands and tools (relative to animals or chairs) activated overlapping regions in left LOTC. The overlap between hand and tool responses in LOTC was found in 27 of the 28 subjects tested (96%), indicating a close correspondence despite differences in visual appearance and object domain (animate vs. inanimate). Hand and tool responses were distinct from nearby object- and motion-responsive regions, indicating that the hand/tool overlap did not reflect a common activation of regions involved in general object processing or (implied) motion. The overlap, close proximity of centers of mass, and multivoxel pattern similarity of tool and hand responses did not extend to nonhand body parts or whole headless bodies, indicating a specific overlap between tools and hands rather than a more general overlap between tools and all body parts. Moreover, the similarity between hand and tool response patterns was specific to a restricted part of left LOTC and was not found in neighboring posterior (OC) or ventral (FG) regions, indicating that the hand/tool overlap in LOTC was not related to low-level visual or shape similarities between hands and tools (which would be expected to equally affect these regions). Finally, functional connectivity analyses, directly contrasting the whole brain connectivity of the hand/tool region with the whole brain connectivity of neighboring body-, motion- and object-selective regions, showed selective functional connectivity between the left hand/tool region and regions in left parietal and left premotor cortex. These fronto-parietal regions have previously been shown to be involved in hand and tool action observation and execution (Bach et al. 2010; Jacobs et al. 2010; Peeters et al. 2009; Valyear and Culham 2010). Taken together, these findings suggest that a primary involvement in object-directed actions, shared by hands and tools, is reflected in the functional organization of OTC.

The overlap between hand- and tool-selective responses in LOTC reported here may be explained by considering specific network connectivity constraints: Form-related object representations have to interact with those brain regions that specify the functional role of the objects (e.g., the left-lateralized fronto-parietal action network). The selective functional connectivity between left LOTC and left fronto-parietal cortex may “force” the representations of both hands and tools to left LOTC, where these representations can most effectively connect to other regions involved in action-related processing. In other words, the functional organization of OTC may partly reflect this region’s functional connectivity pattern to downstream functional networks. Consistent with this interpretation, a recent study, using resting-state functional connectivity analysis, demonstrated intrinsic functional connectivity between tool-selective regions in OTC and fronto-parietal regions implicated in tool manipulation (Simmons and Martin 2011). In the same study, the right fusiform gyrus was functionally connected to a large-scale “social” neural network, raising the possibility that the overlap between bodies and faces in this
region (Peelen and Downing 2005) may similarly be explained by network connectivity constraints. Finally, the effects of handedness on cerebral lateralization have been shown to extend beyond motor and language regions (in frontal cortex) to the functional organization of OTC (Willems et al. 2010), indicating a coupling between the lateralization of interconnected parts of the brain, as predicted by an organization related to functional connectivity patterns.

An alternative explanation for the overlap between hands and tools in LOTC could be that one of these categories indirectly activated the representation of the other category. Thus viewing a picture of a tool may have indirectly activated the representation of hands, or vice versa. On this account, the left LOTC represents just one of these categories (e.g., hands) but is activated by the other category (e.g., tools) through implicit association or visual imagery. However, it should be noted that the stimuli in the present studies were shown in separate blocks and were selected to minimize direct associations between tools and hands: Tool stimuli consisted of isolated pictures of tools that were not currently involved in an action, while the hands were all shown in postures inconsistent with active tool use (Fig. 1). More importantly, our data directly speak against an imagery or association account, for several reasons. First, imagery of an object evokes much weaker responses than directly viewing that object (O’Craven and Kanwisher 2000). Thus if the overlap between hands and tools were to be explained by imagery (e.g., viewing a hammer evokes the percept of a hand), one would expect consistently weaker responses to one of the categories relative to the other. This was not the case. Whereas in the tool region responses to tools were higher than responses to hands (although not significantly different), in the hand region responses to hands were higher than responses to tools (Fig. 3B). Second, one would expect the region defined by imagery or association of a category to be a subset of the region defined by direct viewing of that category. Instead, we found two regions that partly, but not completely, overlapped (Fig. 2). Finally, if visual association (e.g., through the past experience of seeing tools and hands together) caused the hand/tool overlap, we would expect even more overlap between hands and nonhand body parts, or hands and whole bodies (which even included hands), since the hand is itself a body part and seeing hands almost always occurs in association with other body parts (e.g., arms). While nonhand body parts and whole bodies were indeed represented similarly (e.g., Fig. 7C), hands and nonhand body parts (or hands and whole bodies) were not. Therefore, it is unlikely that the hand/tool overlap reported here is fully related to visual imagery or to the visual association of tools and hands. Nevertheless, to conclusively rule out such accounts would require further experiments, for example, comparing responses to tool and nontool objects (e.g., ring, glove) that are matched in terms of their visual association with hands. Finally, research in congenitally blind individuals would provide valuable information regarding the (non)visual nature of the hand and tool representations investigated here.

The close overlap between responses to hands and tools raises the question of whether such responses reflect activation of the same or different neuronal populations, which has implications for the type of representations this region may contain. One scenario is that hands and tools activate a common neuronal population that does not explicitly discriminate between these object types. In this scenario, the hand/tool region could represent a dimension that is common to hands and tools. For example, this region may contain visuo-motor representations of actions (e.g., reflecting hand posture) that can be similarly activated by viewing (or perhaps even moving: Astafiev et al. 2004; Oosterhof et al. 2010; Orlov et al. 2010) hands or tools. A neurophysiology study found evidence for such coding in macaque premotor cortex (F5), by revealing neurons that responded similarly to the grasping of an object with a hand or a tool (Umlita et al. 2008). Alternatively, left LOTC might encode the characteristic rigid motion of tool actions (Beauchamp et al. 2002), although such an account does not readily explain the strong response to hands, which are instead associated with articulated biological motion. Finally, left LOTC may represent semantic information representing action meaning (Kalenine et al. 2010; Martin 2007; Noppeney 2008; Valyear and Culham 2010). Evidence for this view comes from neuropsychological studies showing that lesions to left prefrontal, left parietal, as well as left posterior middle temporal cortex can compromise retrieval of conceptual action knowledge (Campanella et al. 2010; Kalenine et al. 2010; Tranel et al. 2003).

Rather than activating a common neuronal population, it is also feasible that this region contains separate hand- and tool-responsive neurons that are interleaved on a relatively fine spatial scale (below the standard resolution of fMRI). Given their proximity, these interleaved populations would be expected to benefit from similar connectivity with left fronto-parietal regions. Future studies using high-resolution fMRI may be able to address the question of whether hand and tool responses in left LOTC can be dissociated. For example, a previous study showed that face- and body-selective responses in right fusiform gyrus—which overlap at standard scanning resolution—can be separated with high-resolution fMRI (Schwarzlose et al. 2005).

Regardless of the nature of the representations in the hand/tool region—whether these reflect a relatively early perceptual stage or more abstract action-related dimensions—our results indicate that the principles driving the overlap between hands and tools cannot be captured in terms of shared visual properties but instead reflect action-related dimensions. More generally, these results suggest that the functional organization of OTC may partly reflect the organization of downstream functional networks due to regional differences within OTC in the connectivity to these networks.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
AUTHOR CONTRIBUTIONS

Contributions: S.B., C.C.-P., M.L., and M.V.P. conception and design of research; S.B. and M.V.P. performed experiments; S.B. analyzed data; S.B., C.C.-P., M.L., A.C., and M.V.P. interpreted results of experiments; S.B. prepared figures; S.C.-P. and M.V.P. drafted manuscript; S.B., C.C.-P., M.L., A.C., and M.V.P. edited and revised manuscript; S.B., C.C.-P., M.L., A.C., and M.V.P. approved final version of manuscript.

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