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Title: Representational content of occipitotemporal and parietal tool areas

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Abstract: It is now established that the perception of tools engages a left-lateralized network of frontoparietal and occipitotemporal cortical regions. Nevertheless, the precise computational role played by these areas is not yet well understood. To address this question, we used functional MRI to investigate the distribution of responses to pictures of tools and hands relative to other object categories in the so-called "tool" areas. Although hands and tools are visually not alike and belong to different object categories, these are both functionally linked when considering the common role of hands and tools in object manipulation. This distinction can provide insight into the differential functional role of areas within the "tool" network. Results demonstrated that images of hands and tools activate a common network of brain areas in the left intraparietal sulcus (IPS), left lateral occipitotemporal cortex (LOTC) and ventral occipitotemporal cortex (VOTC). Importantly, multivoxel pattern analysis revealed that the distribution of hand and tool response patterns in these regions differs. These observations provide support for the idea that the left IPS, left LOTC and VOTC might have distinct computational roles with regard to tool use. Specifically, these results suggest that while left IPS supports tool action-related computations and VOTC primarily encodes category specific aspects of objects, left LOTC bridges ventro occipitotemporal perception-related and parietal action-related representations by encoding both types of object information.

We thank the reviewers for their insightful comments, which have been very helpful to substantially improve the manuscript. In particular, we are in agreement with regard to points made along the lines of clarity and the appropriateness of the analyses. We have herein sought to address each of the reviewers' comments and have indicated the changes made in the revised manuscript as per below. Furthermore, changes made in the revised manuscript are highlighted in bold.

Reviewer #1: The authors investigated neural activation patterns when participants viewed pictures of tools and hand in comparison to other object categories. The report a considerable overlap in activation for hand and tools in left intraparietal areas, the lateral occipitotemporal cortex and ventral occipitotemporal cortex. Multivoxel pattern analyses showed that the distribution of response patterns for tools and hand differ across these areas. IPS seems to be coding more action-related computations, while VOTC is involved in coding category-specific representations. LOTC seems to encode both types of object representations.

Overall, this is a well-written and fairly straightforward study into the representations of hands and tools. I only have a few comments:

****   P. 9-10: I am not sure whether I follow the 2x5 Contrast x category MANOVA. The contrast is defined by hand (or tool) > nonmanipulable objects, bodies, scrambled images, but these are also included in the category independent measure. Please explain how these two independent measures are calculated.***

The analysis reported in the initial version of our manuscript employed a ROI analysis based upon a so-called 'split-half procedure'. Specifically, upon ROI identification using data from odd runs, parameter estimates were then extracted from even runs, and vice versa. Therefore, parameter estimates used for further statistical tests were independent of the data used for the ROI definition.

Nevertheless, we fully acknowledge (as suggested by reviewer #2) that the scramble objects condition is a preferable control category to define hand and tool ROIs. Indeed, this contrast allows for a more direct comparison of results obtained in univariate and multivariate analyses. Accordingly, we have now re-run the analysis using scrambled objects as a control category for the definition of hand and tool ROIs (methods: page 7; results page 9). In addition, given that the contrast of hands (or tools) relative to scrambled objects is fully independent from the subsequent statistical tests (ergo, it does not require the split-half procedure), to increase our statistical power, we now extract parameter estimates from the average of both runs (see page 7).

****   P. 18-19: I would suggest to omit the link to brain computer interfaces. Decoding attempted or imagined hand gestures requires very different processes compared to merely viewing pictures of hands and tools. I therefore do not agree with the idea that area LOTC might by a good candidate for brain computer interfaces.***

Based on suggestion from both reviewers we revised our discussion section and removed the link to Brain Computer Interfaces (BCI).

Minor comments:
****   Figure 1 caption: "C) Mean parameter estimates for nonmanipulable…" should be "B) Mean parameter estimates for nonmanipulable…"***

****   Figure 2b caption: "light and dark green color-coded cells and light and dark orange color-coded cells are mentioned, but these are not visible in the figure.***

Thank you. We have now corrected for these omissions.

Reviewer #2: Bracci et al. aimed at identifying within occipito-temporal and parietal areas, response properties associated to coding hands vs. tools visual stimuli in order to shed a light into the neural mechanism associated to tools representation in the brain. By analysing patterns of BOLD response associated to viewing different categories of visual stimuli, the authors show that usually considered tools responding regions, such as IPS regions, also, and even more strongly, respond to hand pictures. Hands and tools together activate IPS, a lateral occitotemporal (LOTC) and a ventral occitotemporal (VOTC) region. The authors then applied Multivoxel pattern analysis to identify within those regions pattern

of response dedicated more importantly to code functional vs. categorical (animate vs. inanimate) properties of the stimuli.

Major issues.

1. My main concern is about the choice of the control stimuli to identify hands and tools specific areas and their use in the analyses. Five categories of visual stimuli were used: hands and tools, which are the topic of the study, and bodies, non-manipulable objects and scrambled images, as potential controls.
First, what is the rationale of this choice? I it looks non-manipulable objects should be the direct control for tools, and both these categories are then used as "inanimate" stimuli. On the other hand, the the relationship between hands and bodies is not that obvious. Both are animate stimuli, but bodies, of course, include hands. So what does differentiate the two cathegories? Is the difference in the salience/visibility of the stimuli, the specificity of hands vs. bodies responses? I wonder whether another body, e.g. foot would have been a better control.

Then, I am not sure about the way in which the control stimuli have been used for the analyses. In the ANOVA, the ROIs for hands and tools have been initially defined by contrasting hands- and tool-responses within the averaged response for 3 controls images (page 7). Then, in order to compare hands and tools regions, for each ROI, an 2X5 ANOVA was run with Contrast (Hands, tools) and Category, including all the 5 images. This approach looks at risk of double- dipping. The authors should justify it.

For the MVPA, ROIs were defined by contrasting hands or tools with scramble images. Why different contrasts were chosen for ANOVAs and MVPA? To me, this second approach to select ROIs is safer, pending then excluding scramble images from further analyses.

We agree with the reviewer that the foot is an important control category to define hand-selectivity relative to other body parts and that is why we included the foot in an earlier study (Bracci et al. 2010). At least in our opinion, these earlier analyses assisted to bring some closure to that particular issue. But we are grateful to the reviewer for pointing out that there was an element of ambiguity (i.e., different contrasts used in univariate and multivariate analyses) which could be resolved by using scrambled images as a control which led us to revise our analysis (below).

We apologise for any confusion that gave the reviewer the impression that we were double dipping. We used in fact a split-half procedure for our ROI analysis to address this, but this was also not clear to reviewer #1 (see also response to reviewer #1). Specifically, upon ROI identification using data from odd runs, parameter estimates were then extracted from even runs, and vice versa. Thus, parameter estimates used for further statistical tests were independent of the data used for the ROI definition. This split-half procedure became redundant, however, when we followed this reviewer's suggestion to use scrambled objects as the control.

In the initial version of our manuscript, we chose to use all remaining conditions (bodies, nonmanipulable objects and scrambled objects) as control categories to have a relatively more conservative contrast that would allow us to best define hand and tool responsive regions. We fully agree however that using scrambled objects as the control category for both univariate and multivariate analyses provides a better contrast, thus allowing for a direct comparison of results obtained in the two analyses. We have therefore followed the reviewer's suggestion and have now revised our ROI analysis using scrambled objects as control category for both, the hand (hand vs. scrambled objects) and the tool (tool vs. scrambled objects) contrast (methods: page 7; results page 9). The revised analysis does not affect the findings and our conclusions therefore remain the same as reported in the earlier version of the manuscript.

2. From the MS, it is not clear why MVPA has been conducted to discriminate between action vs. category information, and not also to disambiguate hand and tools activity within the different regions.

We apologize that this point was not sufficiently clear in the first version of the manuscript. Results for within category correlations (hands_run1 – hands_run2) relative to between-category correlations (hands – tools) were reported in the initial version of the manuscript in Figure 2: "*Results from the MPVA analysis revealed that for all object categories, within-category (e.g., hands – hands) correlations were always significantly higher than between-category correlations (e.g., hands – bodies; p < 0.001, for all tests), thus confirming that activity patterns for all categories were reliable and distinguishable from each other within each of the region*." To avoid confusion, we have now moved the above sentence from the figure caption to the main text (see page 11).

3. Results, page 12 lines 40-50. In the IPS ROI, is the comparison between the correlation for action information significant higher than that for category information? The text says that the former is different from 0, and the latter is not, but the direct comparison is not reported, and it grounds one on the main conclusion from this analysis, summarized at page 13. It looks rather obvious that this is the case, but for matter of completeness it would be good to specify.

We took the reviewer's point forward for discussion with a number of colleagues outside the author team and we admittedly realised that our initial choice of quantifying action-related information was rather ambiguous. Indeed, it was not clear what would be the action relationship (1) between two object conditions (tools and nonmanipulable objects) and (2) between two body conditions (hands and bodies). Considering this we have revised the analysis and now define action-related informational content as the difference between hand-object action-related correlations (correlations between hands and tools) minus hand-object non-action correlations (correlations between hands and nonmanipulable objects). Results have been updated accordingly (see pages 11-12). Statistical tests directly comparing action information to category information are now reported for all ROIs on page 12. As per above, the revised analysis does not affect the findings and our conclusions therefore remain the same.

4. Functional connectivity analysis might be also used to study how IPS, LOTC and VOTC regions are connected to each other. This might add important insight for the potential model the authors might propose.

We fully agree with the reviewer's suggestion that additional analyses, such as functional connectivity, could provide relevant information on the functional relationship among IPS, LOTC and VOTC. Unfortunately, we do not have resting state data to perform the abovementioned analysis. We now acknowledge this in the Discussion (see page 15).

5. I understand the focus of the study is on the left hemisphere, as most relevant previous literature focused on it. But it might be informative to show similar analyses for the right hemispheric activations, even if they would provide null-effects. Maybe the distinction between functional vs. category coding would work not only on along the caudal-to-rostral axis with one hemisphere, but also inter-hemisherically.

We thank the reviewer for this suggestion and we agree that this is an interesting point. We have therefore now included the MVPA analysis for regions of the right hemisphere. As in part expected, we observed different results in the right hemisphere, thus suggesting a differential computational role for right IPS and right LOTC. We report these results on page 13 of the Results and Figure 4, and briefly note this difference in the Discussion. However as the reviewer acknowledges the aim of this study is to build on our understanding of the left lateralised tool-network reported in the literature, and we have therefore maintained this same focus in the Discussion. Furthermore, throughout the revised manuscript it has been made explicit where left activation is discussed.

Minor:

Page 12, line 28-29, it would be good to add what the dependent variable on the ANOVA is. It is not transparent from the text.

Thank you, we now clarify this information (see page 12).

A figure showing the different pictures, and some more details about them would be useful (e.g. how many degree of visual angle did they cover? Were they matched for low-level visual information (dimensions, contrast, etc...)?

Thanks for the suggestion. We have now included an additional figure (Figure 1) displaying some examples of the stimuli for each category. In the method section (see page 5), we now report additional information on the images as suggested by the reviewer.

Discussion, page 18-19. I appreciate the link to neuroprosthetics and BCI, and I agree that

understanding how different stimuli are represented beyond the primary sensorimotor cortices is important for the field. However, saying that "the LOTC area may provide all the necessary information for a patient suffering a brain lesions to control a robot hand-and-limb" is a bit too much speculative at this stage.

Reviewer 1 raised the same concern and we have therefore revised the discussion and removed the link to Brain Computer Interfaces (BCI).

***Highlights (for review)**

1) MVPA **showed** representational content differences in regions within the tool network.

2) **Left p**arietal regions encode hand-tool action-related information.

3) Ventral OTC of the tool-network encodes object category information.

4) **Left** lateral OTC encodes hand-tool action-related and category-related information.

5) **Left** lateral OTC bridges ventral OTC (category) and parietal (action) representations.

Representational content of occipitotemporal and parietal tool areas.

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Running title:

The tool-network's representational content.

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Abstract

It is now established that the perception of tools engages a left-lateralized network of frontoparietal and occipitotemporal cortical regions. Nevertheless, the precise computational role played by these areas is not yet well understood. To address this question, we used functional MRI to investigate the distribution of responses to pictures of tools and hands relative to other object categories in the so-called “tool” areas. Although hands and tools are visually not alike and belong to different object categories, these are both functionally linked when considering the common role of hands and tools in object manipulation. This distinction can provide insight into the differential functional role of areas within the “tool” network. Results demonstrated that images of hands and tools activate a common network of brain areas in the left intraparietal sulcus (IPS), left lateral occipitotemporal cortex (LOTC) and ventral occipitotemporal cortex (VOTC). Importantly, multivoxel pattern analysis revealed that the distribution of hand and tool response patterns in these regions differs. These observations provide support for the idea that the **left** IPS, **left** LOTC and VOTC might have distinct computational roles with regard to tool use. Specifically, these results suggest that while **left** IPS supports tool action-related computations and VOTC primarily encodes category specific aspects of objects, **left** LOTC bridges ventro occipitotemporal perception-related and parietal action-related representations by encoding both types of object information.

Key words: tools, action network, occipitotemporal cortex, parietal cortex, fMRI.

Introduction

Tools can be conceptually defined by their specific action-related properties. These properties include the way that a particular tool is grasped and its particular translational profile during action deployment. Neuropsychological data would suggest that the different aspects of tool-related information is processed in anatomically distinct brain regions. For example, lesions in occipitotemporal areas induce profound impairment(s) in object shape recognition and this impairment can even be selective to man-made objects (e.g., tools; see for review Capitani et al., 2003). Nevertheless, the ability to employ unrecognized objects correctly is spared in these patients (Sirigu et al., 1991). Yet a dissociation between a particular object's function and the object's actual manipulation has also been reported; temporal lesions induce loss of conceptual and functional knowledge for manipulable objects (Tranel et al., 2003; Damasio et al., 2004; Kalenine et al., 2010), whereas lesions in the inferior parietal lobule induce substantial impairment in the ability to manipulate objects according to their precise function (Sirigu et al., 1995; Buxbaum et al., 2000; Buxbaum et al., 2007). In accordance with the clinical literature, there is now a vast body of neuroimaging evidence that indicates the existence of a left-lateralized network of tool-selective regions. This network includes the lateral occipitotemporal (Chao et al., 1999), frontoparietal (Chao and Martin, 2000; Mahon, 2013) and ventral occipitotemporal (Chao et al., 1999; Mahon et al., 2007) areas. Although neural activation in these regions has been reported during both perceptual (Martin et al., 1996; Beauchamp et al., 2002, 2003; Beauchamp et al., 2004; Creem-Regehr and Lee, 2005; Creem-Regehr et al., 2005; Downing et al., 2006; Lewis, 2006; Almeida et al., 2013; Gallivan et al., 2013; Mahon et al., 2013; Peelen et al., 2013), and action-related tasks (Choi et al., 2001; Kellenbach et al., 2003; Johnson-Frey et al., 2005; Gallivan et al., 2013), the precise functional role of each of these regions in relation to tool-use is not yet well understood.

It is tacitly understood that two brain areas with different fMRI patterns for two (or more) object categories should then provide for different computational roles. Conversely, a high degree of similarity in response patterns to two (or more) object categories provides support for parallel roles of these same brain areas. In order to disambiguate the computational roles of the different cortical areas within the well-established tool-selective brain regions, we investigated similarities (and differences) across response patterns to tools and hands and compared these with other object categories. The rationale is as follows: tools are inanimate yet action-related objects, whereas hands represent a self-animated body part largely involved in most body-related actions (e.g., object manipulation). Such a distinction can then assist to characterize the functional profile of the regions of the "tool" network. In other words, although hands and tools belong to distinct object domains (animate versus inanimate), these are functionally related within the action domain. We therefore predicted that there would be an overlapping distribution of hand and tool response patterns in brain areas involved in hand-tool action processing. Conversely, in those brain areas that encode object category information the response patterns to hands and tools should be highly distinct, as they are more closely related to the animate or inanimate domains respectively. Such insight would however refine the well-accepted definition of the "tool" network, taking into account the differential computational content of each of the regions within the network.

Material and methods

Participants: Sixteen naive volunteers were functionally scanned (fMRI) in the present study and all participants provided informed consent prior to entering the scanning environment. The study was approved by the Ethical 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. All subjects were determined to be right-handed (Edinburgh Handedness Inventory; Oldfield, 1971). Consequent to excessive head motion being ascertained during post hoc analyses, one participant was excluded from further analyses.

Experimental design and stimuli: The present fMRI study consisted of two functional runs lasting 7 minutes 14 seconds and these corresponding to 217 functional volumes per run. Five distinct conditions were included in the present study: hands, tools, bodies, nonmanipulable objects and scrambled **objects (Figure 1)**. Within each run the five stimulus categories were organized into five pseudo-random sequences of five stimulus blocks, and these were then each interleaved with fixation blocks each lasting 14 s in duration. The fixation blocks also appeared at the beginning and at the end of each run. Within each stimulus block, stimuli were centrally presented for 800 ms with a blank interstimulus interval (ISI) of 200 ms. Each stimulus condition consisted of 70 greyscale images (400 x 400 pixels) on a white background. Stimulus presentation was controlled by a PC computer and the Psychophysics Toolbox software (Brainard, 1997) via Matlab (Mathworks, Natick, MA, USA). The pictures were projected (Canon Xeed SX6 projector) onto a screen located at the foot end of the scanner bed and the screen was viewed through a mirror mounted directly on the head coil. **Stimuli were presented centrally and were each 12° x 12° in visual angle**. All participants performed a 1-back repetition detection task (either 1 or 2 repetitions were presented within a block) in order to ensure that attention was maintained throughout the duration of the fMRI scanning.

Imaging acquisition and preprocessing: All functional and structural images were acquired using a Phillips Achieva 3T scanner with an 8-channel head coil at the Newcastle Magnetic Resonance Centre, University of Newcastle-upon-Tyne (UK). Functional scans were gradient-echo echoplanar T2*-weighted images (EPI). Acquisition parameters were as follows: repetition time (TR) of 2s, echo time (TE) of 30ms, flip angle (FA) of 90 degree, field of view (FoV) of 192 mm and a matrix size of 64 x 64 pixels. Each volume consisted of 30 axial slices with 4.0 mm thickness and with no gap between slices. The structural scans had a TR of 9.6, a TE of 4.6, a FA of 8 deg, a FoV of 256 mm and a matrix of 256 x 208 pixels with 180 slices of 1.0 mm thickness.

Data preprocessing and analyses were performed using Brain Voyager QX (version 2.20; Brain Innovation, Maastricht, The Netherlands) and MatLab (Mathworks, Natick, MA, USA). Preprocessing of the functional data included three-dimensional head-motion correction, linear trend removal, high-pass temporal filtering (cutoff 3 cycles per time course) and spatial smoothing (6-mm full-width half-maximum isotropic Gaussian kernel). For all participants, the functional images were subsequently co-registered to the T1 anatomical images. All of the anatomical images were subsequently transformed into Talairach stereotaxic space. This transformation was applied to the aligned functional data, which was subsequently resampled to 1 mm^3 isotropic voxels.

Statistical analysis: Data were analyzed using a general linear model (GLM) random-effects group-averaged analysis. The GLM model was computed for each participant and this included the 5 conditions of interest and the 6 parameters to account for participant head motion. The fixation blocks represented the baseline condition. The GLM predictors' time courses were modeled using a linear model of the blood-oxygen-level dependent (BOLD) hemodynamic response using the default Brain Voyager QX "two-gamma" function. Prior to computing the GLM analysis, all functional runs were further z-normalized.

In the region-of-interest (ROI) analysis, the tool- and hand-responsive ROIs were identified in each individual subject **in the left hemisphere by comparing pictures of hands (or tools) versus pictures of scrambled objects**. Our statistical activation maps were thresholded at $p < 0.005$ (uncorrected) and these ROIs were restricted to a 20 mm^3 cube centered on the voxel with the highest signal peak. **When no active voxels were found at this threshold, a more liberal threshold of p < 0.01 was applied. For each condition and for each ROI, p**arameter estimates were **extracted from the** average **of both runs (run 1 and run 2)** and then further tested using analyses of variance (ANOVAs) and post-hoc pairwise t-tests. In LOTC, both the tool and the hand contrast could be localized in all participants. **Conversely, in IPS and VOTC, both contrasts could not be defined in three participants.** These participants were therefore excluded from the ROI analysis in each of these ROIs.

Correlation-based multivoxel pattern analysis (MVPA; Haxby et al., 2001) was carried out to investigate the similarity in the response patterns to hands, tools, bodies and nonmanipulable objects in all of the identified ROI-based occipitotemporal and parietal tool areas. For the MVPA analysis, ROIs were defined in the intraparietal sulcus (IPS), lateral occipitotemporal (LOTC) and ventro occipitotemporal (VOTC) cortex in both hemispheres contrasting (at the group level) hands, tools, bodies and nonmanipulable objects relative to scrambled objects (uncorrected threshold, $p < 0.001$). These ROIs were demarcated by selecting all active voxels within a cube of 30 mm width centered on the voxel with the highest peak activation. For each participant, parameter estimates were extracted for each voxel and each condition, separately for run 1 (odd) and run 2 (even). Multivoxel activity patterns for each stimulus category in run 1 were then correlated with multivoxel activity patterns for each stimulus category in run 2 and vice versa. The resulting correlations were then Fisher transformed $\{0.5 \times \ln[(1 + r)/(1 - r)]\}$ and averaged across the two run-wise comparisons (e.g., hands even – tools odd and tools even – hands odd). The scrambled objects condition was excluded from the analysis because this condition was used as a baseline for ROI definition. The resulting 4 x 4 correlation matrix for each subject and ROI provides an estimate of the neural similarity of the four object categories. Correlations were quantified via ANOVAs and pairwise t-tests.

Results

Single subject ROIs analysis

Consistent with previous research on the neural representation of tools (Chao and Martin, 2000; Lewis, 2006; Valyear and Culham, 2010; Bracci et al., 2012), the tool contrast (tools > scrambled objects) revealed a left-lateralized network of areas that comprised the IPS, LOTC and VOTC (Figure **2a, purple** color-coded). Similarly, the hand contrast (hands > scrambled objects) revealed hand responses – partially overlapping with the tool responses in the left IPS, left LOTC and left VOTC (Figure **2a, blue** color-coded). Figure **2**a shows partially overlapping responses to hands and tools in the lateral and ventral occipitotemporal and parietal areas in the left hemisphere of four representative participants. Table 1 reports single-subject average peak activation coordinates for these contrasts of interest. It is further noted that we observed hand-related activations in the corresponding occipitotemporal and parietal areas of the right hemisphere. However, given that overlapping tool- and hand-related activations were consistently localized within the left hemisphere only, the following analyses were constrained to the left hemisphere only.

We subsequently examined for possible similarities in the profile of partially overlapping hand and tool regions (Material and Methods), separately for each ROI (VOTC, LOTC and IPS). Parameter estimates for each condition were extracted from each contrast in each individual subject and tested in a 2 x **4** ANOVA with Contrast (hand, tool) and Condition (hands, tools, bodies, nonmanipulable objects) as the within-subject factors. Results revealed a significant Contrast x Condition interaction ($F_{(3,33)}$ = **8.23**; $p < 0.001$, see Figure **2**b) in IPS. Post hoc t-tests **revealed differential functional profiles for** IPS-hand and IPS-tool. **In IPS-hand, the hand condition** elicited the highest response, as compared to all other categories ($p < 0.001$, for all tests). Notably, within the IPS-tool, **the response to hands and tools did not differ from each**

other (p = 0.54), and both elicited significantly higher response relative to **the remaining** conditions (p < 0.0**3**, for all tests).

In LOTC, **the 2 x 4 ANOVA with Contrast (hand, tool) and Condition (hands, tools, bodies, nonmanipulable objects) as the within-subject factors** revealed a significant Contrast x Condition interaction ($F_{(3,42)} = 6.13$; $p < 0.001$, see Figure **2**b). Post hoc testing revealed that in both LOTC-hand and LOTC-tool responses to hands were highest compared to all other categories (p < 0.0**3**, for all tests). **In both ROIs**, responses to tools were significantly higher than nonmanipulable objects (p < 0.00**2**, for all tests), but were **significantly** lower than bodies (p < 0.**006, for all tests**).

As for IPS and LOTC, in VOTC the 2 x 4 ANOVA with Contrast (hand, tool) and Condition (hands, tools, bodies, nonmanipulable objects) as the within-subject factors revealed a significant interaction of Contrast x Condition ($F_{(3,33)} = 21.42$; $p < 0.001$, see Figure **2**b). **Post hoc t-tests revealed differential functional profiles for VOTC-hand and VOTC-tool. In VOTC-hand responses to hands and bodies did not differ from each other (p = 0.20), and both conditions were significantly higher that the remaining conditions (p < 0.001, for all tests).** In VOTC-tool responses to **all conditions were significantly higher than baseline (p < 0.001, for all tests), but pairwise comparisons did not reveal differences across all conditions (p > 0.36, for all tests)**. An overview of all post hoc t-tests carried out and their corresponding p-values (corrected for the number of comparisons) are listed in Table 2.

Taken together, these results demonstrate that within the left hemisphere of the healthy human cortex, hands and tools activate partially overlapping regions not only in LOTC (Bracci et al., 2012) but also in IPS and VOTC. Moreover, the higher response to hands relative to tools suggests that the well-accepted definition of the human “tool” network should be refined to also considering that these same areas respond first and foremost to hands.

Multivoxel pattern analysis

Having established the extent of hand/tool overlap by means of the above analysis, we can now further investigate and compare the representational content of the different regions within this network via multivoxel pattern analysis. To frame this in another way: the greater the similarity in the activity patterns of two areas the tighter or more comparable their likely information or computational processing roles. In order to investigate the representational content of parietal and occipitotempomporal hand/tool regions, we compared the distribution of responses to depictions of hands and tools as two object categories that are functionally associated within the action domain, yet largely distinct within the object domain (animate versus inanimate). We predicted high similarity in the distribution of hand and tool response patterns **(relative to hands and nonmanipulable objects)** in action processing areas. Conversely, in those cortical brain areas that encode category-specific information of objects we would predict response patterns of hands and tools to cluster according to their particular object-domain, respectively (animate and inanimate).

To this aim, we employed correlation-based MVPA (Haxby et al., 2001). As for the ROI analysis, based upon the observation that overlapping hand and tool responses were observed in the left hemisphere, only left hemisphere regions were initially included in the MVPA analysis. **Initial results revealed that for all object categories, within-category (e.g., hands – hands) correlations were always significantly higher than between-category correlations (e.g., hands – bodies; $p < 0.001$, for all tests), thus confirming that activity patterns for all categories were reliable and distinguishable from each other within each of the region (Figure 3a). Subsequently, f**or each ROI (Material and Methods), we quantified the degree to which the representational content is indicative of object *category* information (animate/inanimate division) and object *action* information (hand-object action properties). In order to quantify the information with regard to object category, for each ROI, we subtracted the average of the between-domain correlations (Figure **3**b; light green color-coded cells for correlations between one animate condition and one inanimate condition) from the average of within-domain correlations (Figure **3**b; dark green color-coded cells for correlations between either two animate or two inanimate conditions). For each ROI, hand-object action-related information was identified by subtracting the average of hand-object non-action correlations (Figure **3**b; light orange color-coded cells for correlations between **hands and nonmanipulable objects**) from **the average of hand-**object action-related correlations (Figure **3**b; dark orange color-coded cells for correlations between **hands and tools**). Within-condition correlations (Figure **3**b; cells along the diagonal) were excluded from these calculations. The bar graphs presented in Figure **3**b depict the degree to which the representational content in **left** IPS, **left** LOTC and **left** VOTC reveals *category* information (green color-coded) and *action* information (orange color-coded) of objects.

Subsequently, **for each subject and for each ROI, correlations for** *category* information and *action* information were tested in a further 3 x 2 ANOVA with ROI (**left** IPS, **left** LOTC, **left** VOTC) and Information (Category, Action) as within-subject factors. Results revealed a significant ROI x Information interaction ($F_{(2, 28)} = \mathbf{66.30}$; $p < 0.001$; Figure **3**b), thus suggesting differences in the information content of each of these ROIs. These conclusions were confirmed with post-hoc analyses, which revealed the following results. In **left** IPS, action-related information was significantly greater than zero ($t_{14} = \mathbf{3.65}$; $p < 0.0\mathbf{03}$), whereas information content about object category (animate and inanimate entities) did not significantly differ from zero ($t_{14} < 1$; $p = 0.\mathbf{45}$). **Furthermore, in this region action-related information was significantly higher than category information ($t_{14} = 2.13$; $p = 0.05$).** In contrast, in **left** LOTC both action and category information was significantly different from zero ($t_{14} > 4$; $p < 0.001$, for both tests) and, moreover, these values did not significantly differ from one another ($t_{14} < 1$; $p = 0.$**69**). Lastly, in **left** VOTC, **the correlation that quantified the categorical information was significantly greater compared to the correlation that quantified the action information ($t_{14} = 14.98$; $p < 0.001$), and only** information for category was significantly greater than zero ($t_{14} =$ **6**.**24**; $p < 0.001$)**.**

Next, to investigate whether or not this organization is uniquely left lateralized, we performed the same analysis for IPS, LOTC and VOTC in the right hemisphere (Figure 4). As for the left hemisphere, for each subject and for each ROI, correlations for *category* information and *action* information were tested in a 3 x 2 ANOVA with ROI (right IPS, right LOTC, right VOTC) and Information (Category, Action) as within-subject factors. Results revealed a significant ROI x Information interaction ($F_{(2, 28)} = 19.70$; $p < 0.001$; Figure 4b). Subsequent post-hoc analyses revealed different results from those observed in the left hemisphere. In right IPS, neither *category* information nor *action* information differed from baseline (t < 2, for both tests). Furthermore, as compared to the left LOTC, in right LOTC we did not observed any evidence for action information. Instead, in this ROI, the information for category was significantly higher than information for action ($t_{14} = 9.00$; $p < 0.001$). Finally, similar to left VOTC, significantly higher information content for category relative to action was observed in right VOTC ($t_{14} = 13.92$; $p < 0.001$).

In summary, the present analyses revealed both similarities and differences in the distribution of response patterns to hands and tools across the parietal and occipitotemporal regions **in the left hemisphere**. Specifically, the activity patterns in IPS cluster according to object action-related information, whereas in VOTC activity patterns cluster most prominently according to category-related information of objects. Most interestingly, LOTC that encodes *both* the action- and category-related properties of the objects could be argued to act as an effective computational bridge for the parietal and ventral occipitotemporal computations. **This organization appears to be specifically left lateralized.**

Discussion

Functional neuroimaging studies have consistently reported that viewing tools, such as a hammer or a screwdriver, induces activation in the left fronto-parietal and occipitotemporal areas (see for review, Lewis, 2006). The present investigation sought to expand upon these earlier investigations by describing and comparing the representational content of the distinct areas within the tool network. This was accomplished via the identification of any similarities in their response pattern distributions to pictures of tools and hands, compared to other object categories – specifically, bodies and nonmanipulable objects. It is noteworthy that hands and tools differ in visual appearance and object domain, yet these object categories are closely related within the action domain – as both hands and tools are employed in order to carry out skillful and dexterous prehensile actions. Here we predicted that those areas that may be preferentially involved in the processing of hand-object action-related information would show similarities in their subsequent distribution of hand and tool response patterns. Conversely, the distribution of hand and tool representations should dissociate in areas devoted to the processing of category-specific information for animate and inanimate entities.

Initial results from the ROI analysis revealed that, similar to tools, images of hands activated a network of areas in parietal, lateral occipitotemporal and ventral occipitotemporal cortical areas. These results confirm and expand on our previous report (Bracci et al., 2012) showing that hand-related responses were observed not only in left LOTC but also in left IPS and in VOTC. Moreover, the higher response to hands compared to tools in IPS and LOTC provides evidence to suggest that the purported well-accepted definition of a “tool” network should now be refined to take into account that these areas respond first and foremost to hands.

Furthermore, the results of the MVPA analysis showed that despite hands and tools inducing activation across a similar modular network of parietal and occipitotemporal brain areas, there were some differences in information content in the IPS, LOTC and VOTC. Perhaps most notably, the activity patterns in **left** LOTC revealed significant information for *both* action and category domains, with high response pattern similarities observed for categories that share action-related properties (hands and tools) but also for entities that correspond to the same object domain (animate and inanimate). **Such a functional organization was not observed in the right hemisphere.** We therefore conclude that **left** LOTC conjoins these two distinct modular networks (action and objects, specifically) and may represent a computational hub for effective integration across these two functionally distinct cortical processing pathways.

The activity patterns in the **left** IPS revealed significant information only for object action-related properties. Strikingly, and in contrast to the IPS, VOTC primarily encodes object category-related information. These results provide new insight into the computational role(s) of the regions of the already established tool network. Whereas **left** IPS is argued to underpin the implementation of tool-hand interactions (Chao and Martin, 2000; Gallivan et al., 2013), VOTC is known to represent aspects of object category-specific knowledge (e.g., animate vs. inanimate; Martin et al., 1996; Martin, 2007; Mahon et al., 2009). Finally, the computational role of **left** LOTC might be that of associating information processed in VOTC and IPS as here we provide evidence that this cortical area encodes both action- and category-related information, which might be fundamental in order to fully recognize and consequently execute dexterous hand-tool prehensile motor movements. **Future work employing functional connectivity analyses could further clarify connectivity patterns among IPS, LOTC and VOTC.**

The similarities observed between LOTC and IPS response patterns**, were only present in the left hemisphere (Figure 3 and 4). Thus, in agreement with clinical studies on tool-use** (Johnson-Frey et al., 2005; Buxbaum and Kalenine, 2010; Kalenine et al., 2010; Buxbaum et al., 2014) **these results suggest that these areas compute action properties common to both**

hands and tools. Furthermore, previous literature has provided evidence that the left LOTC and the left IPS are computational nodes within a network that underlies skilled hand-object interaction, and when damaged can consequently result in precise deficits in object-specific manipulation skill-sets while nevertheless affording the ability to grasp objects in response to their specific structural content (Sirigu et al., 1995; Buxbaum et al., 2003; Ietswaart et al., 2006). Further evidence supporting the common involvement of LOTC and IPS in complex hand-object interactions is based on neuroimaging studies. These studies report co-activation of these areas when participants imagine or pantomime tool-use (Grezes and Decety, 2002; Rumiati et al., 2004; Creem-Regehr and Lee, 2005; Johnson-Frey et al., 2005; Arbib et al., 2009), when observing grasping movements toward tools (Creem-Regehr and Lee, 2005), or when planning to grasp either with the hand or with a novel mechanical tool (Arbib et al., 2009).

Yet, despite these similarities, representational content in **left** LOTC and **left** IPS also revealed differences. The observation that both regions encode object action-related information but only LOTC carries information of object category suggests that the latter might encode –in addition to hand-object action properties— semantic and or/ visual information with relevance for action understanding. Consistent with this idea, neuropsychological evidence has demonstrated that disruption of occipitotemporal areas affects both action-related knowledge in tool-gesture comprehension (i.e. distinguishing between hammering and sawing; Kalenine et al., 2010), and semantic knowledge affecting structural (i.e. body shape) and/or semantic coding of the body (Schwoebel et al., 2004; Moro et al., 2008). Conversely, left parietal lesions can selectively disrupt dynamic coding of body parts' intrinsic positions (Buxbaum et al., 2000) and movement amplitude essential to tool-use (Kalenine et al., 2010).

Tool-use understanding requires computing information with regard to the hand posture and grip configuration relative to a particular tool. This computation requires understanding of whether the hand is correctly shaped in relation to the tool's physical features (e.g., handle of a hammer) as well as the tool's specific functional utility. This interpretation is consistent with a recent functional neuroimaging study (Vingerhoets et al., 2013) that reported activation in left LOTC and left anterior IPS when participants were required to judge whether or not a specific hand posture (e.g., precision grip) matched the functional use of a given tool (e.g., car keys). To summarize, the current evidence from the literature together with the present findings suggest a partially common but also a somewhat differential role for **left** IPS and **left** LOTC in respect to hand-tool interactions.

Our results are consistent with the vast clinical literature reporting differential impairment of category-specific conceptual knowledge for animate and inanimate objects following focal lesions in ventral temporal cortex (see for review, Caramazza and Shelton, 1998; Capitani et al., 2003). We observed that object responses in VOTC clustered according to object category information. This animate-to-inanimate division that encompasses the ventral surface of the inferior temporal cortex (Konkle and Caramazza, 2013) has been documented across species (Kriegeskorte et al., 2008) and is independent of visual experience (Mahon and Caramazza, 2009). Information content in this region is associated with the specific conceptual knowledge (Martin, 2007), form, size (Haxby et al., 2001; Op de Beeck et al., 2008; Konkle and Oliva, 2012) and surface properties (Cavina-Pratesi et al., 2010b, a) of objects.

Previous imaging studies investigating category selective responses in inferior temporal cortex reported selectivity for faces and bodies in lateral VOTC (Peelen and Downing, 2005; Schwarzlose et al., 2005). Whilst there was a clear significant degree of overlap in cortical activation across these specific categories, high-resolution fMRI did dissociate functional specificity for these precise categories (Schwarzlose et al., 2005). The present study expands upon these earlier conclusions by demonstrating that selectivity for hands may also be present in VOTC where we report significant within- relative to between-category correlations for both hands and bodies (Figure **3**a). This latter result, suggests that the response patterns for these two categories where highly distinguishable in VOTC. Future studies designed to investigate the fine-grained organization within the VOTC area and in relation to hands, bodies and faces are necessary. One possibility, analogous to what was recently reported for LOTC (Orlov et al., 2010), could be that VOTC houses a topographic organization of representations for all the different body parts.

As noted in the introduction, selectivity for tools has been consistently reported both in ventromedial OTC (Martin et al., 1996; Chao et al., 1999; Mahon et al., 2007) and in lateral OTC (Chao et al., 1999; Beauchamp et al., 2002, 2003; Bracci et al., 2012; Bracci and Peelen, 2013). The present findings demonstrate differences in the representational/computational content/roles of these regions. While VOTC processes information with regard to the object category, LOTC processes information for *both* action- and category-related properties of objects. One possible argument for the latter finding is that in LOTC the representations of objects, we perform actions with, partially overlap with the hand representations because of their close relationship with one another in both the action domain (both hands and tools participate in goal directed actions) and the object domain (tools can become an extension of the body; Bracci and Peelen 2013).

In conclusion, we report a comprehensive network of overlapping hand-related and tool-related responses comprising of LOTC, IPS and VOTC **in the left hemisphere**. Interestingly, MVPA revealed a distinct pattern of representational content for each of these regions, thus suggesting differential computational roles for regions of this network. Specifically, while parietal regions are involved in the processing of hand-object action-related information, ventral occipitotemporal cortical areas are involved in the processing of category-specific information.

Remarkably, computations in LOTC by encoding both types of object information may represent a computational hub for effective integration across ventro occipitotemporal perception-related and parietal action-related representations.

Table 1. Single-subject mean Talairach coordinates for the hand and the tool contrast. Single-subject mean Talairach coordinates (see Figure **2**a) are reported for the hand contrast [(hands > scrambled objects) and the tool contrast [(tools > scrambled objects) (p = 0.005 uncorrected).

Contrasts	**x**	**y**	**z**
Hands > scrambled objects			
Left IPS	**-36**	**-45**	**46**
Left LOTC	**-46**	**-72**	**-5**
Left VOTC	**-42**	**-46**	**-17**
Tools > scrambled objects			
Left IPS	**-41**	**-42**	**43**
Left LOTC	**-46**	**-74**	**-8**
Left VOTC	**-38**	**-47**	**-19**

Table 2: Individual ROI analysis statistical overview. Overview of individual ROI parameter estimates pairwise t-tests including t-values and uncorrected *p*-values for each ROI (IPS-hand, IPS-tool, LOTC-hand, LOTC-tool, VOTC-hand, VOTC-tool). Bold characters indicate *p*-values that survived correction for multiple comparisons. Only contrasts for hands and tools relative to the remaining conditions (nonmanipulable objects and bodies) are reported.

ROIs		*Conditions*		
		Tools	*Bodies*	*Nonmanipulable objects*
IPS-hand	*Hands*	t =8.90; *p* < **0.001**	t =9.52; *p* < **0.001**	t =14.92; *p* < **0.001**
	Tools		t =7.50; *p* < **0.001**	t =2.27; *p* = 0.045
IPS-tool	*Hands*	t =0.63; *p* = 0.540	t =2.53; *p* = 0.028	t =2.89; *p* = 0.015
	Tools		t =3.82; *p* = **0.003**	t =4.67; *p* = **0.001**
LOTC-hand	*Hands*	t =12.09; *p* < **0.001**	t =3.55; *p* = **0.003**	t =11.95; *p* < **0.001**
	Tools		t =-6.01; *p* < **0.001**	t =4.34; *p* = **0.001**
LOTC-tool	*Hands*	t =7.37; *p* < **0.001**	t =2.31; *p* = 0.036	t =9.24; *p* < **0.001**
	Tools		t =-3.21; *p* = **0.006**	t =3.75; *p* = **0.002**
VOTC-hand	*Hands*	t =10.37; *p* < **0.001**	t =1.36; *p* = 0.198	t =5.93; *p* < **0.001**
	Tools		t =-6.49; *p* < **0.001**	t =0.72; *p* = 0.483
VOTC-tool	*Hands*	t =0.66; *p* = 0.522	t =-0.42; *p* = 0.688	t =-0.29; *p* = 0.773
	Tools		t =-0.95; *p* = 0.365	t =-0.55; *p* = 0.596

Figure captions

Figure 1. Experimental stimuli. For each experimental condition (nonmanipulable objects, tools, hands, bodies, and scrambled objects) 6 (out of 70) images are presented.

Figure 2. Individual-subject activation maps and ROI analysis for the hand and tool contrast. A) Individual-subject hand-responsive regions (blue color-coded; [hands > scrambled objects]), and tool-responsive regions (purple color-coded; [tools > scrambled objects]) are shown in left IPS, left LOTC and left VOTC in four representative participants at the threshold $p = 0.005$ uncorrected. C) Mean estimates for nonmanipulable objects, tools, hands and bodies are shown in left IPS (hand and tool), left LOTC (hand and tool) and left VOTC (hand and tool). ROIs were restricted to a cube of 20 mm width centered on the activation peak (threshold $p < 0.005$, uncorrected). Error bars indicate SEM.

Figure 3. Multivoxel pattern analysis (MVPA) in the left hemisphere. A) Multivoxel correlation matrices in left IPS, left LOTC and left VOTC, as functionally defined in each individual subject upon contrasting the average response to all object categories (nonmanipulable objects, tools, hands and bodies) relative to scrambled objects. Each cell of the matrix represents a correlation value (averaged across subjects). B) Bar graphs show *category* information and *action* information in IPS, LOTC and VOTC in the left hemisphere. Information about object category was computed by subtracting the average of between-object domain correlations (light green color-coded cells for correlations between one animate condition and one inanimate condition) from the average of within-object domain correlations (dark green color-coded cells for correlations between either two animate or two inanimate conditions). Information about object action was computed by subtracting the average of hand-object non-action correlations (light orange color-coded cells for correlations between hands and nonmanipulable objects) from the average of hand-object action-related correlations (dark orange color-coded cells for correlations between hands and tools). Error bars indicate SEM.

Figure 4. Multivoxel pattern analysis (MVPA) in the right hemisphere. A) Multivoxel correlation matrices in right IPS, right LOTC and right VOTC, as functionally defined in each individual subject upon contrasting the average response to all object categories (nonmanipulable objects, tools, hands and bodies) relative to scrambled objects. Each cell of the matrix represents a correlation value (averaged across subjects). B) Bar graphs show *category* information and *action* information in IPS, LOTC and VOTC in the right hemisphere. Information about object category was computed by subtracting the average of between-object domain correlations (light green color-coded cells for correlations between one animate condition and one inanimate condition) from the average of within-object domain correlations (dark green color-coded cells for correlations between either two animate or two inanimate conditions). Information

about object action was computed by subtracting the average of hand-object non-action correlations (light orange color-coded cells for correlations between hands and nonmanipulable objects) from the average of hand-object action-related correlations (dark orange color-coded cells for correlations between hands and tools). Error bars indicate SEM.

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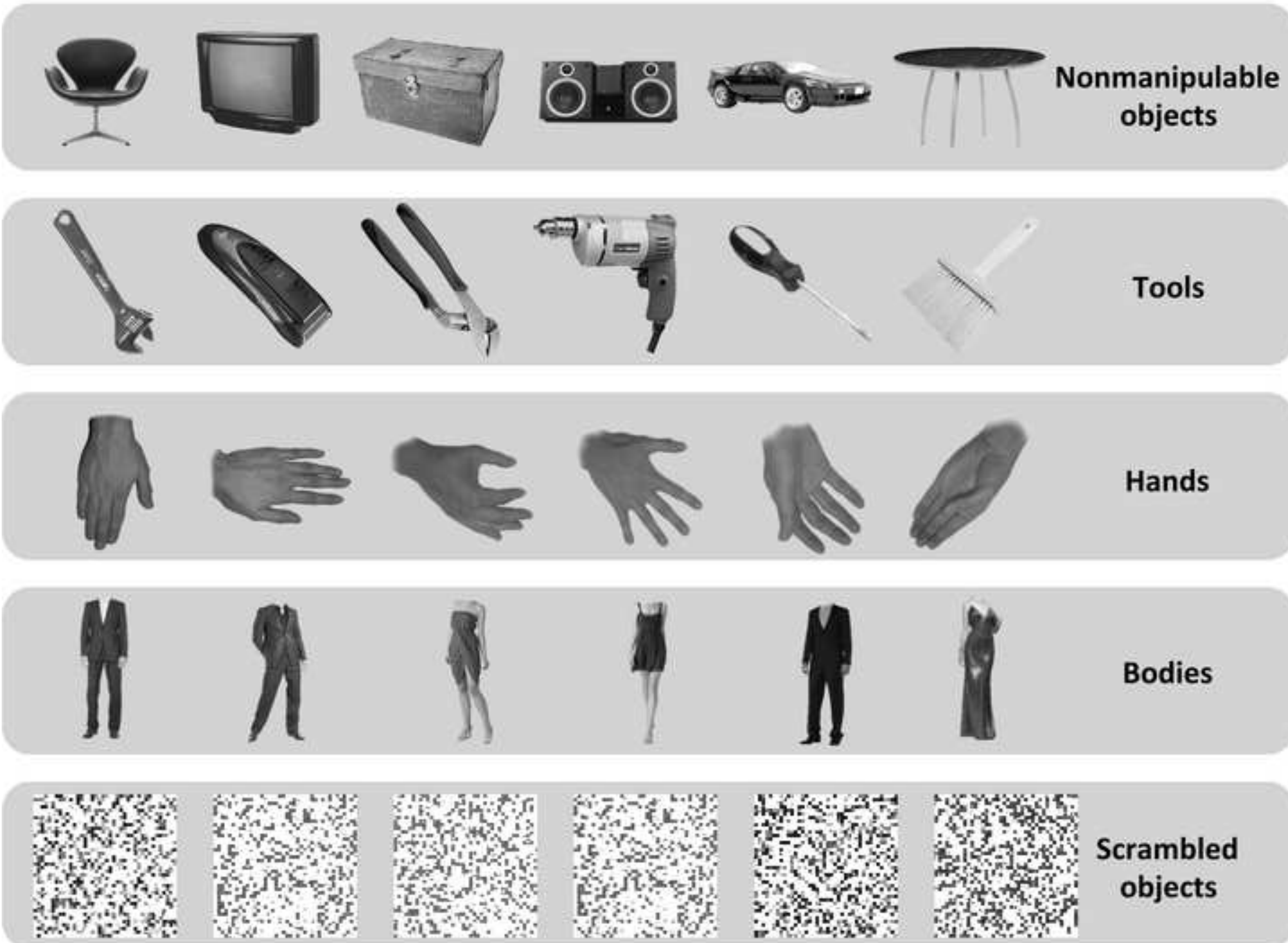

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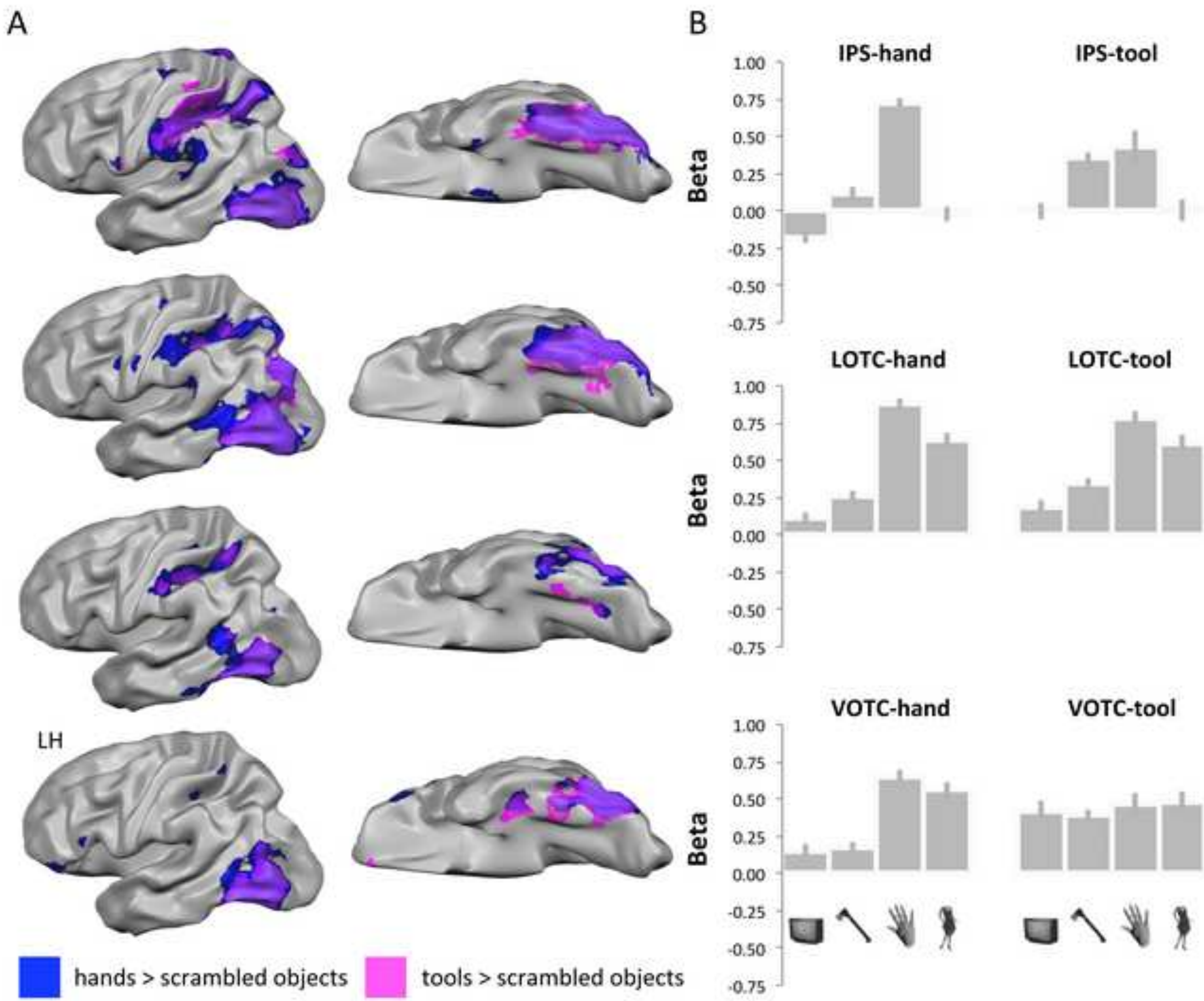

Figure 3
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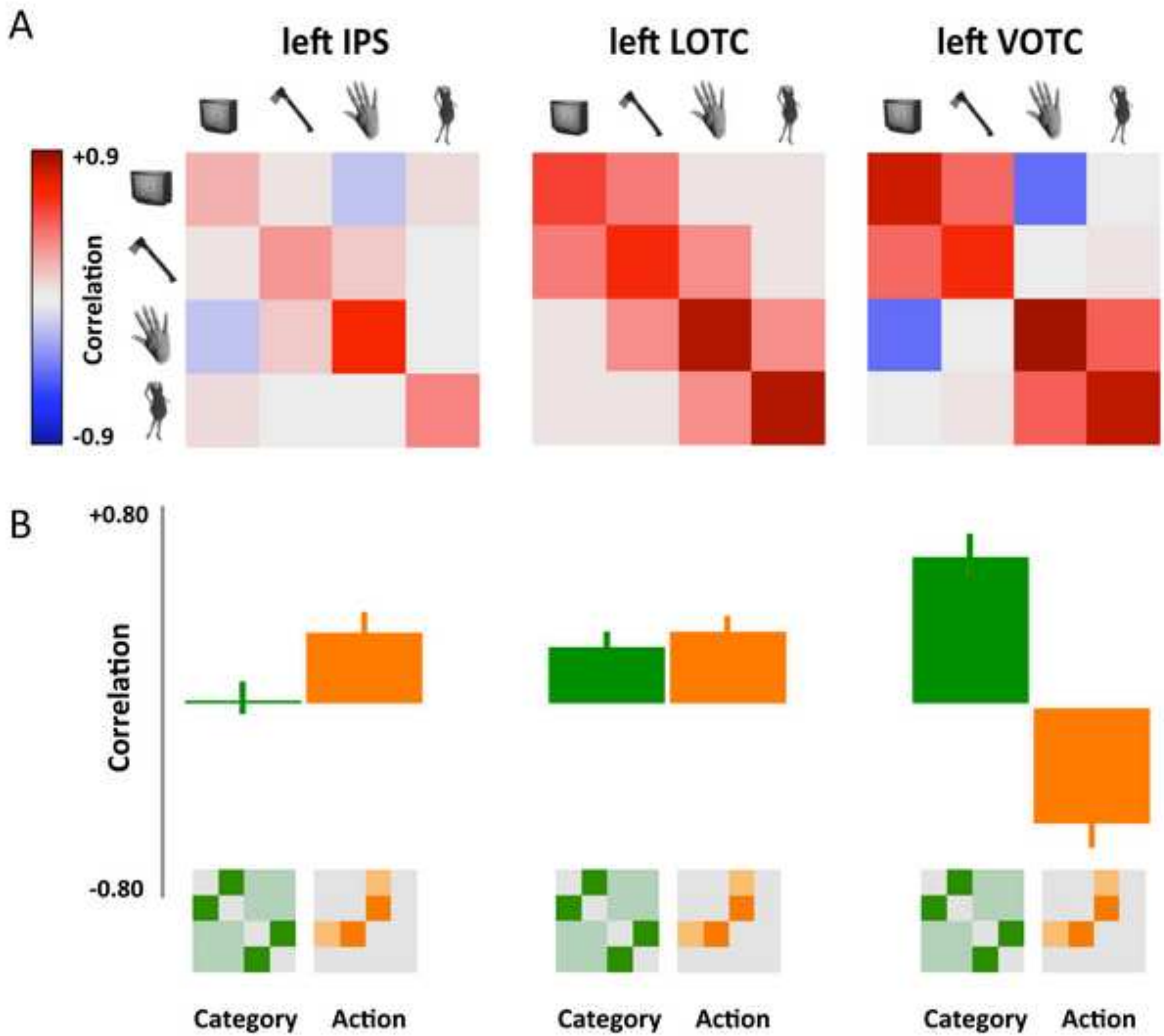

Figure 4
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