ORIGINAL ARTICLE

Voluntary Actions Modulate Perception and Neural Representation of Action-Consequences in a Hand-Dependent Manner

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Abstract

Evoked neural activity in sensory regions and perception of sensory stimuli are modulated when the stimuli are the consequence of voluntary movement, as opposed to an external source. It has been suggested that such modulations are due to motor commands that are sent to relevant sensory regions during voluntary movement. However, given the anatomical-functional laterality bias of the motor system, it is plausible that the pattern of such behavioral and neural modulations will also exhibit a similar bias, depending on the effector triggering the stimulus (e.g., right/left hand). Here, we examined this issue in the visual domain using behavioral and neural measures (fMRI). Healthy participants judged the relative brightness of identical visual stimuli that were either self-triggered (using right/left hand button presses), or triggered by the computer. Stimuli were presented either in the right or left visual field. Despite identical physical properties of the visual consequences, we found stronger perceptual modulations when the triggering hand was ipsi- (rather than contra-) lateral to the stimulated visual field. Additionally, fMRI responses in visual cortices differentiated between stimuli triggered by right/left hand. Our findings support a model in which voluntary actions induce sensory modulations that follow the anatomical-functional bias of the motor system.

Key words: efference copy, fMRI, sensory modulation, voluntary actions

Introduction

Perception is a process that does not depend solely on the physical properties of the stimulus, but rather on complex interactions between those physical properties and the neural state of the perceiver. Therefore, the same stimulus can be perceived differently each time, depending on context. For example, when presented with bi-stable stimuli (such as the Rubin vase-face illusion or the Necker cube), perception fluctuates over time although the physical properties of the stimulus remain unchanged (Hesselmann et al. 2008; Iemi et al. 2017). Modulations of neural states, and subsequent perception, have been shown to depend on various contextual variables such as attention (as in the cocktail party effect; Arons 1992),

stimulation history (first vs. repeated stimulation; Grill-Spector et al. 2006; Krekelberg et al. 2006), and expectancy (Näätänen and Kreegipuu 2011; Todorovic et al. 2011).

An important factor that has been shown to shape the neural state in sensory regions, and perception of sensory stimuli, is voluntary movement (Schütz-Bosbach and Prinz 2007; Hughes et al. 2013; Reznik and Mukamel 2019). Previous studies have shown that when sensory stimuli are the consequence of voluntary movement, evoked neural responses and perceptual reports are modulated relative to neural and perceptual responses to identical stimuli triggered by an external source (Hughes et al. 2013). A classic example for this effect comes from the tactile domain, where self-initiated (vs. externally initiated) tactile

stimuli are perceived as less intense (Blakemore et al. 1999; Kilteni and Ehrsson 2017) and evoke less activity in somatosensory cortex (Blakemore et al. 1999; Kilteni and Ehrsson 2020). Similar modulations were found in the auditory (Baess et al. 2009; Lange 2011; Reznik et al. 2015b) and visual domains (Stenner et al. 2014; Yon and Press 2017; Mifsud et al. 2018). Notably, although the majority of studies suggest that voluntary actions attenuate perception or neural responses (e.g., Blakemore et al. 1998; Weiss et al. 2011; Dewey and Carr 2013), there is also increasing evidence for conditions in which voluntary actions enhance such responses (e.g., Hughes and Waszak 2011; Ackerley et al. 2012; Reznik et al. 2014). In the visual domain, behavioral and neural modulations have been reported with respect to the perception of stimulus intensity (Cardoso-Leite et al. 2010; Mifsud et al. 2016; Yon and Press 2017; Csifcsak et al. 2019), movement speed and direction (Dewey and Carr 2013; Desantis et al. 2014), and detection of temporal delays (Matsuzawa et al. 2005; Benazet et al. 2016; van Kemenade et al. 2016); however, across studies, the directionality of these modulations is not consistent, showing no clear tendency toward enhancement or attenuation (Schwarz et al. 2018).

With respect to the underlying mechanism, it has been suggested that modulations of self-triggered sensory stimuli are driven by copies of the motor commands that are sent from the motor system during voluntary movement ("efference copies") to sensory regions (Wolpert et al. 1995; Wolpert and Miall 1996). It is speculated that such signals convey information to relevant sensory regions regarding the expected sensory outcome and modulate their neural state, resulting in differential processing of the actual reafferent (sensory) signal when it finally arrives. Efference copies have been suggested to play an important functional role in various domains such as the sense of agency (Gentsch and Schutz-Bosbach 2011; Burin et al. 2017; Haggard 2017); however, despite important basic and clinical implications ascribed to such signals (Pynn and DeSouza 2013; Shergill et al. 2014), their underlying neuroanatomical source and mechanism is poorly understood.

Within the motor system, neural activity in some regions is strongly lateralized, while in other regions, neural activity is more balanced. For example, activations in primary motor cortex and the cerebellum are strongly lateralized—with neural activity in a particular cerebral/cerebellar hemisphere usually associated with control of contralateral/ipsilateral limbs, respectively (Kalaska and Rizzolatti 2013). Conversely, neural activity in premotor cortex and the supplementary motor area show a weaker laterality bias—with more balanced neural activity during control of ipsi/contra lateral limbs (Horenstein et al. 2009). Given the premise that the source of efference copies resides within the motor regions generating the action, it is plausible that the degree of sensory modulations would exhibit significant differences that depend on the identity of the stimulus-triggering hand. Such differences, if found, would better support a neuroanatomical source of efference copies in motor regions that exhibit a strong bias to hand identity. Furthermore, such differences would suggest that information conveyed by the motor pathways to sensory regions during voluntary movement is not restricted to the sensory consequences of the action but also contains information regarding the triggering effector. Therefore, probing hand-dependent differences in sensory modulations at the behavioral and neural levels may provide important insight with respect to the underlying mechanism and potential functional role of such signals. Indeed, in the auditory modality, we have recently reported perceptual and neural differences in the magnitude of sensory modulations that depend on the sound-triggering hand (right/left). Specifically, modulations in left/right auditory cortex were stronger if it resided within the same hemisphere as the active motor cortex generating the sound (Reznik et al. 2014).

In light of these results, we hypothesized that different stimulus-triggering hands, engaging different motor pathways, will elicit different sensory modulations at the neural level that might also manifest as different perceptual reports. In the current study, we examined the hemispheric bias of sensory modulations in the visual domain, using behavioral and neural measures (fMRI) in healthy participants. To this end, we manipulated the relationship between the stimulated visual field (right vs. left visual field), causal agent generating the stimulus (self/external), and identity of the effector participants used to trigger the stimulus (right/left hand).

Methods

Participants

Thirty-three participants, naïve to the purposes of the study, were recruited. All participants were healthy, right handed (self-report), and had normal or corrected to normal vision. Only participants who successfully completed the behavioral part of the study were asked to continue to an fMRI session (see below). The study conformed to the guidelines that were approved by the ethical committee in Tel-Aviv University and the Helsinki Committee of the Sheba Medical Center. All participants provided written informed consent to participate in the study and were compensated for their time.

Behavioral Session

In order to assess the sensory modulation of self-generated visual stimuli, participants were engaged in a two alternative forced choice (2AFC) task regarding the brightness level of two identical visual stimuli, triggered either by the participant or the computer.

In each trial, participants were presented with two visual stimuli in a consecutive manner (one "passive" and one "active"). A trial began with a change in the color of the fixation point from dark gray to white, which cued the appearance of the first ("passive") visual stimulus 500 ms later. The stimulus was a gray circle, 2.5° in diameter that appeared for 400 ms either 2.5° to the right or to the left of a fixation point (1 × 1°) (see Fig. 1A). After the "passive" stimulus disappeared, participants were instructed to press a button using their index finger in order to trigger the second ("active") stimulus (presented for 400 ms). Participants were instructed which hand to use (right/left) at the beginning of each block and no temporal constrain was imposed. Participants' hands were located on a response box throughout the experiment, which was located on a desk below the screen, at the midline of their body. After the active stimulus disappeared, participants were requested to report which stimulus was brighter, by pressing one of two buttons with the hand opposite to the one they used to trigger the active stimulus. Participants were instructed to answer as best as they can and to guess if they cannot see any difference between the stimuli. Unbeknownst to the participants, both stimuli (passive/active) were identical. In order to ensure that participants were attending the stimuli and performing the task, in 10% "catch trials" there was a real
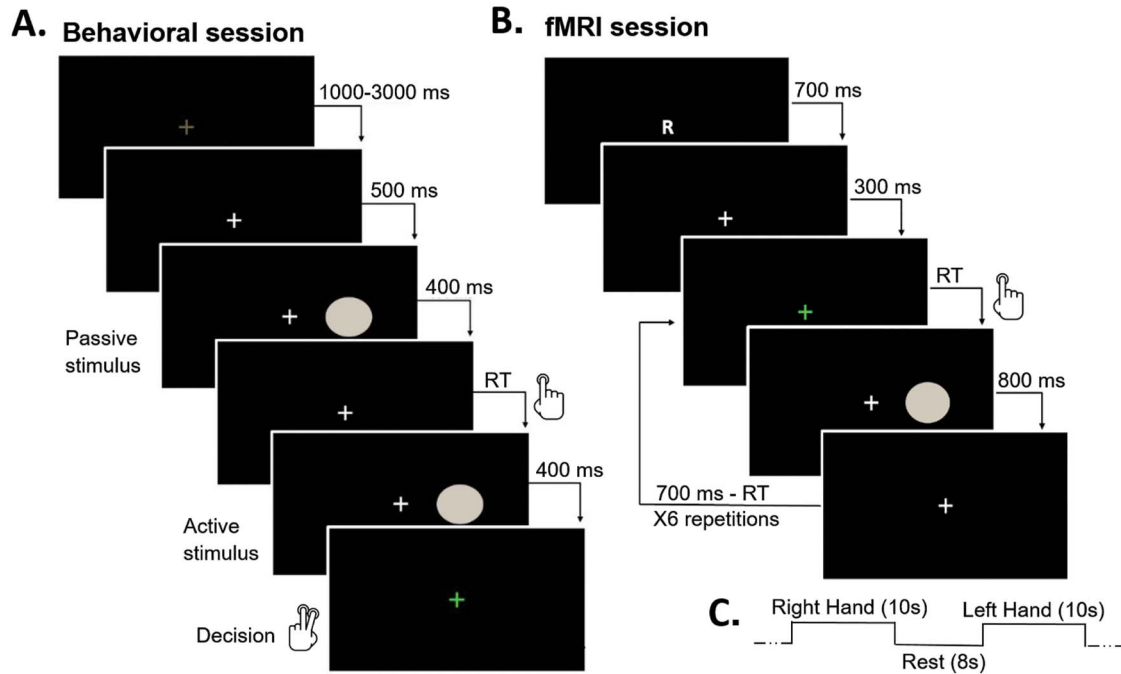
Figure 1. Experiment procedure for behavioral and fMRI sessions. (A) Behavioral session design: example of a single trial from a right-hand right visual-field block. Participants reported which stimulus was brighter using the other hand (left in this example). (B) fMRI session design: example from a right-hand block in a right visual-field run. (C) Block design scheme for fMRI experiment. Within each run, the order of right and left hand blocks was randomized while stimulated visual field was kept constant.

difference of 30% in brightness in which performance could be assessed. Intertrial interval was randomized between 1 and 3 s. All stimuli were presented on a 24′ screen using Psychtoolbox-3 (www.psychtoolbox.org) on MATLAB 2015b (The MathWorks, Inc.). This procedure was similar to the one applied by Reznik et al. (2015a) in the auditory modality.

Participants performed a total of four blocks corresponding to the two visual fields and two hands used to trigger the active stimulus (one block per condition). An important function ascribed to efference copies is that they convey information regarding expected sensory consequences. Therefore, we maintained a consistent mapping between action (button press) and its visual consequences in separate experimental blocks. Before each block, participants were informed about the stimulated visual field and which stimulus-triggering hand to use. These were kept constant throughout the block. Block order was counter-balanced across participants. Each block contained 60 trials (6 of which were "catch trials"). Participants with accuracy rates lower than 75% in the "catch trials" were disqualified from further analysis on the grounds of poor performance. In order to keep participants engaged throughout the experiment, they were informed that they will receive performance feedback relative to previous participants after two blocks and at the end of the experiment. Performance was assessed based on accuracy in the "catch trials" during the experiment. Participants with accuracies above/below 75% on catch trials were given "Above Average" or "Below Average" performance feedback, respectively.

Before each experimental block, participants went through a short training block of 12 trials in order to establish the mapping between button press (right/left hand) and sensory outcome (right/left visual field). Four of these training trials were "catch

trials" in which incorrect responses were followed by feedback in the form of a red "X" appearing on the screen. Otherwise, correct responses on catch trials or any response on trials with identical stimuli were simply followed by the next trial. During experimental blocks, participants did not receive immediate feedback on incorrect responses to catch trials.

Eye-tracking data were recorded using SMI RED-m 500-Hz eye-tracker (SensoMotoric Instruments GmbH) and were analyzed in real-time using iViewX API for MATLAB. In the eye-tracker calibration procedure, eye-tracking accuracy was kept below 0.7°. Participants were instructed to fixate on the fixation cross throughout the experiment and were informed that breaking fixation will result in trial disqualification and the addition of another trial to the block. Any eye movement larger than 1.5° from the fixation point during stimulus presentation triggered a "fixation break" screen, followed by the re-initiation of the trial. Due to technical problems, eye-tracking data from two participants were not obtained.

fMRI Session

Participants who successfully completed the behavioral session were invited to participate in an fMRI session. The aim of this session was to examine whether neural activations in visual cortex, evoked by action-triggered visual consequences, depend on the stimulus-triggering hand. To this end, participants triggered identical visual stimuli using either their right or left hand. The fMRI session included 8 functional runs and 1 anatomical run. Throughout all functional runs, participants were requested to fixate on a cross (1 × 1°) in the middle of the screen. The first two functional runs were used to localize visual areas associated with right and left visual fields. During these

runs, participants were instructed to fixate, while a flickering checkerboard appeared either on their right or left visual field. The checkerboard flickered at 10 Hz (size 12.6 × 11.2°) in order to get robust activations in a large part of the visual pathway. The checkerboard appeared for 6 s and then disappeared for 8 s of rest, repeating for a total of 16 times in each run (8 per visual field). The order of right and left visual field stimulation was randomized. We used two identical runs instead of one long run in order to minimize fixation breaks due to participants' fatigue.

The other 6 functional runs were designed to examine differential activity evoked by visual stimuli triggered with the right versus left hand (experimental runs). These runs were organized in a block design, consisting of 10 s blocks separated by 8 s of resting period, during which a fixation cross appeared on a black screen. Each run consisted of 16 blocks, 8 per triggering hand. In each experimental run, the stimulated visual field was kept constant (either right or left visual field condition), while the triggering hand changed across blocks. Overall, participants performed 3 runs for each visual field. Participants were informed that during the run, they will be instructed to press a button either with their right or left hand and that their presses will trigger a visual stimulus, a gray circle similar to the ones presented on the behavioral session, either on the right or left visual field. Similar to the behavioral paradigm, visual stimuli were 2.5° in diameter and appeared 2.5° either to the right or left of a fixation cross. Stimuli were presented on a 32′ monitor and viewed by the participants through a mirror placed on the MRI head coil.

Each block started with a 700-ms presentation of either the letter "R" or "L" (0.5 × 0.5°) on the center of the screen, indicating the hand to be used for triggering the visual stimulus during the block (right or left, respectively). After the letter disappeared, participants were instructed to press with the appropriate hand as fast as possible every time the fixation point changed color to green (once every 1.5 s; see Fig. 1B). Prior to each experimental run, participants were informed that each button press will trigger a visual stimulus in a specific location (which was kept constant throughout the run: either right or left visual field). Overall, participants triggered six visual stimuli on each block. Each stimulus was presented immediately after the button press for 800 ms. If the participant's reaction time (RT) was longer than 700 ms, a red "X" (1.4°) appeared on the screen, indicating slow responses, and the entire block was removed from further analysis. This measure was taken in order to maintain a constant presentation pace in both right- and left-hand conditions and to make sure blocks were precisely timed to TR. Order of right and left hand blocks within each run was randomized.

In order to keep participants attentive to the visual stimuli, in some blocks (two or four blocks in each run), one of the circles was blue instead of gray. Participants were requested to count how many times they saw a blue circle throughout the run and verbally report it at the end of each run. Blocks with blue circles were removed from further analysis.

Throughout the experiment, participants' eye movements were monitored in order to ensure fixation. Eye-tracking data were collected using an MR-compatible Eyelink 1000 plus (SR Research Ltd.), sampled at 500 Hz. Eye-tracking calibration accuracy was kept below 1°. Blocks with fixation breaks (eye movement larger than 1.5° from the fixation point during stimulus presentation) were discarded from further analysis.

fMRI Data Acquisition

Functional imaging was performed on a Siemens Magnetom Prisma 3T Scanner (Siemens Healthcare) with a 64-channel head coil at the Tel-Aviv University Strauss Center for Computational Neuroimaging. In all functional scans, an interleaved multiband gradient-echo echo-planar pulse sequence was used. 66 slices were acquired for each volume, providing whole-brain coverage (slice thickness 2 mm; voxel size 2 mm isotropic; TR = 2000 ms; TE = 30 ms; flip angle = 82°; field of view = 192 mm; acceleration factor = 2). For anatomical reference, a whole-brain high-resolution T_1-weighted scan (slice thickness 1 mm; voxel size 1 mm isotropic; TR = 2530 ms; TE = 2.99 ms; flip angle = 7°; field of view = 224 mm) was acquired for each participant.

Data Analysis

Behavioral Session

In order to evaluate the behavioral magnitude of sensory modulation, a modulation index was calculated for each combination of triggering hand and stimulated visual field. This index was defined as the absolute difference between the proportion of trials in which the participant chose the self-triggered stimulus as brighter, and chance level of choosing either stimulus as brighter (active/passive; 0.5), as in the formula below:

$$\text{Modulation index} = |\,\%\text{active brighter} - 50\%\,|.$$

This measure represents the deviation from chance for each participant to report the stimulus from one condition (active/-passive) as brighter. A modulation index of 0 indicates an equal proportion of trials in which the active or passive stimulus was reported as brighter. Note that this index is nondirectional and emphasizes the magnitude of deviation irrespective of the tendency to report, for example, the active condition as brighter (or vice versa). Importantly, we used this index to compare changes in report tendency across conditions rather than examine general tendency biases to report one condition as brighter. This index was used as the dependent variable in the analysis of the behavioral session. Behavioral data were analyzed using a 2 × 2 repeated measures ANOVA with stimulated visual field (right vs. left) and stimulus triggering hand (ipsilateral vs. contralateral to stimulated visual field) as independent variables. Analysis was performed using JASP (JASP Team, 2019. Version 0.10.1).

fMRI Session

fMRI data preprocessing and first-level GLM analysis were conducted using the FMRIB's Software Library's (FSL v5.0.9) fMRI Expert Analysis Tool (FEAT v6.00) (Smith et al. 2004a). The data from each experimental run underwent the following preprocessing procedures: brain-extraction, slice-time correction, high-pass filtering at 100 s (0.01 Hz), motion-correction to the middle time-point of each run, smoothing with a 5-mm FWHM kernel, and correction for autocorrelation using prewhitening (as implemented in FSL). We excluded from further analysis participants with more than one run during which the absolute displacement values exceeded 2 mm. All images were registered to the high-resolution anatomical data using boundary-based reconstruction and normalized to the Montreal Neurological Institute (MNI) template using nonlinear registration.

Localizer data were analyzed using a general linear model with two regressors—right visual field and left visual field. A conventional double gamma response function was convolved with each of the regressors in order to account for the known lag of the hemodynamic responses. Additionally, the six motion parameter estimates from the rigid body motion correction were included in the model as nuisance regressors. We calculated both right visual field > left visual field and left visual field > right visual field contrasts. Results from these contrasts were FWE-corrected for multiple comparisons with $\alpha = 0.05$.

The six experimental runs were analyzed using a multivoxel pattern analysis (MVPA) classifier, in a searchlight approach within the visual ROI defined from the functional localizer runs. We used a Java implementation of a support vector machine (SVM) classifier (Chang and Lin 2011) to discriminate right- and left-hand activation patterns in the visual cortex. For each voxel and each block, we calculated percent signal change of the last TR (5th TR from block onset), relative to time course mean. This resulted in a total of 40 values for each voxel in each participants' brain (20 right hand and 20 left hand in each visual field). The exact number of values varied slightly across participants (minimum 18 per condition) due to response errors in the task (slow responses, using the wrong hand or fixation break). Within participant, the number of values across conditions was kept equal by randomly choosing values from the condition with more trials. For each voxel, defined as center-voxel, we outlined a neighborhood, which included the center voxel and its 26 closest voxels (in Euclidean distance).

To estimate classification level between right- and left-hand blocks within a certain visual field, we used an SVM classifier with a linear kernel ($C = 1$, gamma = 1/27) and a leave-one-block-out from each condition (right/left hand) approach. In case of 20 blocks/condition, an exhaustive separation of train/test trials would have resulted in $20 \times 20 = 400$ possible combinations. Due to computational reasons, for each neighborhood, we computed classification accuracy across 250 iterations in which we randomly chose one block value from each condition for our leave-out test-set. The averaged accuracy level on the test-set across all 250 iterations was assigned as the decoding accuracy of the center voxel. In order to determine the significance level of our classification values, we used permutation analysis to create a shuffle distribution for each neighborhood of voxels. For each participant, we shuffled the data labels (right/left hand blocks) and repeated the same analysis that was performed on the real data. Overall, for each participant, we obtained a map of real data accuracy-levels and 100 maps of accuracy-levels based on shuffled data. To determine group-level significance, we used the permutation scheme suggested by Stelzer et al. (2013). First, we averaged all the real accuracy-level maps across subjects to create a group average map. Next, we randomly chose one shuffle map from each participant and averaged those shuffled maps across participants to create one average shuffled map. The second step was repeated 10 000 times, providing a distribution of shuffled data accuracy maps. Thus, the minimal P-value of the real map is 0.0001. Finally, the P-values obtained from this procedure were corrected for multiple comparisons using false discovery rate approach (Benjamini and Hochberg 1995) with $q = 0.05$.

Functional Connectivity Analysis

In order to examine functional connectivity between visual and motor cortices and between visual cortex and the cerebellum,

we calculated the correlation between the time courses in these regions. For each participant, we defined separately the cerebellum, motor, and visual regions in both hemispheres. Visual regions of each participant were defined by GLM contrast of each visual field condition's experimental runs, using the contrast (right hand + left hand) > rest, in order to ensure that we cover areas responsive to the visual stimulus regardless of triggering hand. In order to restrict our ROI to visual cortex, the results of this contrast were intersected with the visual localizer (using a contrast of right visual field > left visual field or left visual field > right visual field to examine left/right visual cortices, respectively). For correlation analysis, we used the averaged time course from the most significant voxel in the ROI and its 26 nearest neighbors. Motor regions and cerebellum of each participant were defined using a GLM contrast of each visual field condition's experimental runs, using the contrasts right hand > left hand and left hand > right hand. We intersected the results from these contrasts with the anatomical masks of right and left motor cortex taken from the Harvard-Oxford lateralized cortical structural atlas (Desikan et al. 2006) and with a cerebellum mask taken from the MNI structural atlas (Mazziotta et al. 2001). As in the visual cortex, for correlation analysis, we used the averaged time course from the most significant voxel in the ROI and its 26 nearest neighbors. Thus, ROI size across regions was identical and determined in a subject-specific manner. Next, for each visual cortex time course (right/left hemisphere), we calculated the Pearson correlation with the time course of left and right motor cortex separately, and left and right cerebellum separately. To compare between correlations of each stimulated visual cortex with ipsilateral and contralateral motor cortex and cerebellum across subjects, we used a paired t-test applied on the Fisher's transformation of the correlation values.

Results

Perceptual Modulation: Behavioral Results

Data from five participants were excluded from further analysis due to low performance on the behavioral task (see Methods), leaving data from 28 participants (11 males, mean age 24.41, range 18–30 years). Examining participants' responses regarding stimulus brightness, averaged across all conditions, we found no consistent direction of modulation, with some participants reporting active stimuli as darker (20/28) and the rest as brighter (8/28).

In order to examine the influence of stimulus-triggering hand on the magnitude of perceptual modulations, we used a 2 × 2 repeated measures ANOVA ($N = 28$) on the modulation index (see Methods), with visual field and triggering hand (ipsilateral or contralateral to visual field) as independent variables. We found a significant main effect for triggering hand ($F(1,27) = 4.85$, $P = 0.03$; see Fig. 2A for group analysis and Fig. 2B for individual subjects data), indicating higher modulation index for stimuli triggered with the hand ipsilateral to the stimulated visual field ($M = 0.16$, SD = 0.07), relative to identical stimuli triggered with the hand contralateral to the stimulated visual field ($M = 0.13$, SD = 0.08). We did not find a significant main effect of stimulated visual field (right visual field: $M = 0.14$, SD = 0.10; left visual field: $M = 0.15$, SD = 0.09; $F(1,27) = 0.80$, $P = 0.38$) or a significant interaction between stimulated visual field and triggering hand ($F(1,27) = 0.153$, $P = 0.699$). Separate analysis of the group of participants reporting active stimulus as brighter and group of participants reporting the active stimulus as darker than the
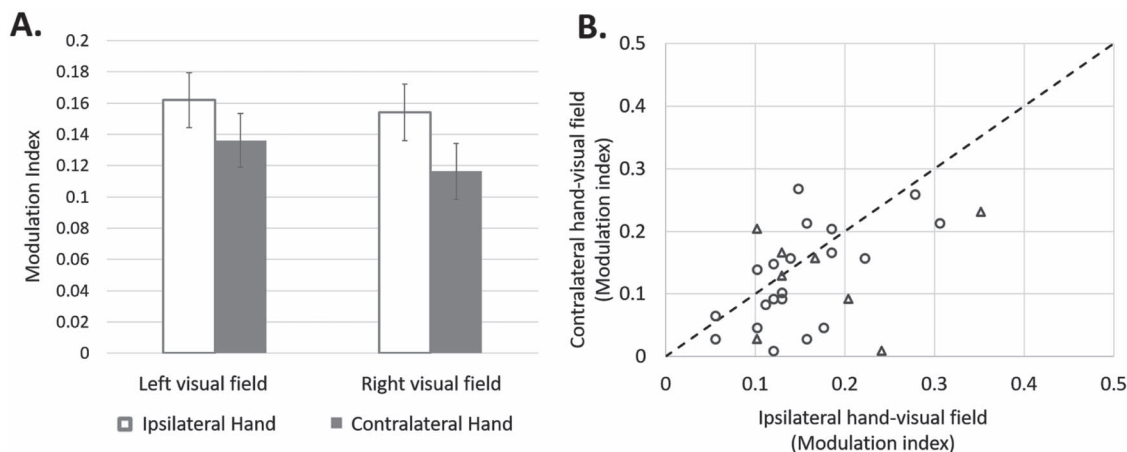
Figure 2. Hand-dependent modulation of perception. (A) Perceptual modulations (group analysis). Modulation index ($N = 28$) according to visual field of action consequences shows a significant main effect for laterality of triggering hand (ipsilateral vs. contralateral to the stimulated visual field) ($F(1,27) = 4.85$, $P < 0.05$). Note that in the right visual field, the ipsilateral triggering hand is the right hand, while in the left visual field, the ipsilateral triggering hand is the left hand. Error bars represent SEM across subjects. (B) Modulation index of individual subjects according to laterality of triggering hand (ipsilateral/contralateral). Each dot represents the averaged modulation index of each participant collapsed across visual fields. Circles represent participants tending to report the active stimulus as darker than the passive stimulus and rectangles represent participants tending to report the active stimulus as brighter. Dashed line represents equal magnitude of modulation for ipsilateral/contralateral conditions.

passive stimulus (circles/triangles in Fig. 2B) yielded a similar pattern of results (see Supplementary Materials for full analysis).

Comparing RTs for triggering the active stimulus, we did not find a main effect for visual field (right visual field: $M = 0.67$ s, $SD = 0.40$; left visual field: $M = 0.64$ s, $SD = 0.29$; $F(1,27) = 0.38$, $P = 0.55$) and no main effect for triggering hand (ipsilateral hand: $M = 0.64$ s, $SD = 0.27$ s; contralateral hand: $M = 0.66$ s, $SD = 0.31$ s; $F(1,27) = 0.35$, $P = 0.56$). Additionally, we did not find a significant interaction effect between visual field and triggering hand (right visual field: ipsilateral hand—$M = 0.62$ s, $SD = 0.28$ s, contralateral hand—$M = 0.73$ s, $SD = 0.52$ s; left visual field: ipsilateral hand—$M = 0.67$ s, $SD = 0.32$ s, contralateral hand—$M = 0.60$ s, $SD = 0.26$ s; $F(1,27) = 3.10$, $P = 0.09$). Average performance on "catch trials" across participants was high in all conditions (mean accuracy across conditions = 95.24%). Overall, participants maintained fixation and out of 288 valid trials/participant; the median number of trials that had to be repeated was 11 (range 1–37 across participants) throughout the experiment.

fMRI Results

Out of the 28 participants who successfully completed the behavioral study and were recruited to the fMRI session, two participants requested to terminate the fMRI experiment before data collection was completed and four other participants had large head movements during the scan and therefore were excluded from the fMRI analysis. Thus, fMRI analysis was conducted on data from the remaining 22 participants (9 males, mean age 24.23, range 18–30 years). Participants successfully maintained fixation during the experiment and no blocks were discarded.

Visual ROIs

In order to functionally define the visual cortex, we first performed a visual localizer task (see Methods). We used GLM with a contrast of right visual field > left visual field to define regions sensitive to visual stimulation in either right or left

visual fields. Figure 3A shows a multisubject ($N = 22$), MNI normalized, Boolean map of significant voxels with either positive (red) or negative (blue) contrast values ($P < 0.05$ Bonferroni corrected; 3852 voxels). This map was used as a mask to define visual regions in the experimental runs.

Neural Modulations in Visual Cortex According to Triggering Hand: SVM Results

In order to examine differential modulation of visual cortex, we classified fMRI activity patterns evoked by identical visual stimuli according to triggering hand (right/left). Our group analysis revealed neighborhoods of voxels significantly distinguishing between the two hand conditions both in right visual field runs (blue voxels) and in left visual field runs (red voxels) ($P < 0.05$ FDR corrected; Fig. 3B). Significant differentiation was found in both visual cortices, regardless of the stimulated visual field (see Fig. 3B). In the right visual field condition, we found 206 significant neighborhoods, 60 of which were in the left (contralateral) visual cortex. In the left visual field condition, we found 268 significant neighborhoods, 149 of which were in the right (contralateral) visual cortex. About 23 neighborhoods overlapped between right and left visual field conditions (purple voxels in Fig. 3B). Individual decoding accuracy levels and their mean across participants are shown in Figure 3C.

In order to examine differences in RTs between right and left hand, we used a 2×2 repeated measures ANONA with triggering hand (right/left) and stimulated visual field (right/left) as independent variables. We did not find a main effect for triggering hand (right hand: $M = 0.39$ s, $SD = 0.07$ s; left hand: $M = 0.39$ s, $SD = 0.06$; $F(1,21) = 0.41$, $P = 0.53$) and no main effect for stimulated visual field (right visual field: $M = 0.38$ s, $SD = 0.08$ s; left visual field: $M = 0.39$ s, $SD = 0.05$ s; $F(1,21) = 1.27$, $P = 0.27$). Furthermore, we did not find a significant interaction effect between visual field and triggering hand (right visual field: right hand—$M = 0.38$ s, $SD = 0.08$ s, left hand—$M = 0.38$ s, $SD = 0.09$; left visual field: right hand—$M = 0.39$ s,
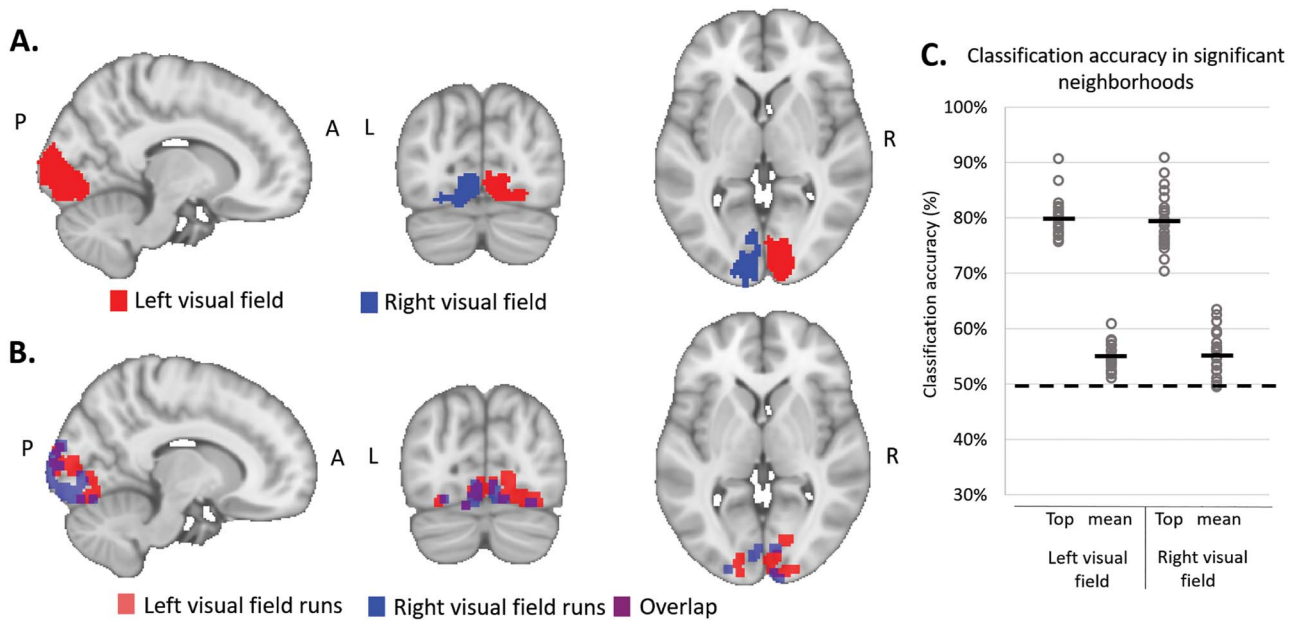
Figure 3. Hand-dependent modulations of fMRI signals. (A) Boolean map showing significant voxels in visual cortex obtained from the localizer runs (GLM analysis, $n = 22$; $P < 0.05$ Bonferroni corrected; see Methods section). Red voxels represent significant voxels in the contrast left visual field > right visual field and blue voxels for the opposite contrast. (B) Classification analysis (group results). Boolean map of significant voxel neighborhoods separating right and left hand in visual cortex, despite identical visual stimuli ($P < 0.05$ FDR corrected; see Methods). Red voxels correspond to voxels from left visual field runs and blue voxels correspond to voxels from right visual field runs. Purple areas represent significant voxel neighborhoods decoding right/left hands in both visual field runs (overlap of red and blue voxels). Note the significant voxels discriminating hands in both hemispheres irrespective of stimulated visual field. P—posterior, A—anterior, R—right hemisphere, L—left hemisphere. (C) Individual subjects' classification accuracy levels in significant voxels for each stimulated visual field condition. Significant voxels were identified from the group decoding analysis (see Methods). Top represents the decoding accuracy level of the center-voxel with highest decoding accuracy in each participant, and mean represents the mean decoding accuracy across all significant voxels (defined at the group level), for each participant. Dashed line represents chance accuracy level (50%).

SD = 0.06, left hand—M = 0.39 s, SD = 0.05 s; $F(1,21) = 0.016$, $P = 0.90$).

GLM Results

In addition to the SVM analysis, we also conducted a GLM analysis in order to examine whether we can find any consistent differences in signal direction between conditions across subjects. Therefore, we calculated the contrasts right hand > left hand and left hand > right hand in each visual field condition. After correcting for multiple comparisons (using FDR correction), we did not find significant voxels within the visual ROI to any of these contrasts.

Connectivity between Stimulated Visual Cortex and Motor Regions

In order to examine whether motor regions exert stronger modulations on sensory regions residing within the same hemisphere, we calculated the correlations between activity in each visual cortex with activity in right/left motor cortices and right/left cerebellum. We found that in left visual field runs, activity in the right visual cortex was more strongly correlated with the right (within hemisphere) motor cortex ($r = 0.32$) than with the left (across hemisphere) motor cortex ($r = 0.27$; $t(21) = 2.29$, $P = 0.03$). In right visual field runs, we found no significant difference in correlation between left visual cortex and left (within hemisphere; $r = 0.23$) or right (across hemisphere; $r = 0.25$) motor cortices ($t(21) = 0.81$, $P = 0.43$; see Fig. 4). The interaction of correlation values between stimulated visual

cortex (right/left) and motor cortex (ipsilateral/contralateral to stimulated visual field) approached significance ($F(1,21) = 4.14$, $P = 0.055$). In this analysis, we also found a marginally significant effect of stimulated visual cortex, such that the right visual cortex showed a stronger connectivity with both motor cortices ($M = 0.31$, SD = 0.13) than the left visual cortex ($M = 0.25$, SD = 0.11; $F(1,21) = 3.65$, $P = 0.07$). We found no main effect of motor cortex (ipsilateral motor cortex: $M = 0.29$, SD = 0.13; contralateral motor cortex: $M = 0.27$, SD = 0.11; $F(1,21) = 0.94$, $P = 0.34$).

A similar connectivity analysis performed between stimulated visual cortex and right/left cerebellum showed no significant effect of laterality: in left visual field runs, connectivity between right visual cortex and right ($r = 0.18$) or left ($r = 0.21$) cerebellum ($t(21) = 1.46$, $P = 0.16$); and in right visual field runs, connectivity between left visual cortex and left ($r = 0.18$) or right ($r = 0.18$) cerebellum ($t(21) = 0.11$, $P = 0.91$). Examining the interaction in correlation values between stimulated visual cortex (right/left) and cerebellum (ipsilateral/contralateral to the stimulated visual cortex), we found no significant interaction effect ($F(1,21) = 1.39$, $P = 0.25$) or main effects (visual cortex: $F(1,21) = 1.42$, $P = 0.25$; cerebellum: $F(1,21) = 1.22$, $P = 0.28$).

Discussion

In the current study, we examined differences in perceptual and physiological responses to identical visual stimuli while manipulating the stimulus-triggering hand. Our behavioral findings show stronger perceptual modulation for stimuli triggered with the hand ipsilateral (vs. contralateral) to the stimulated
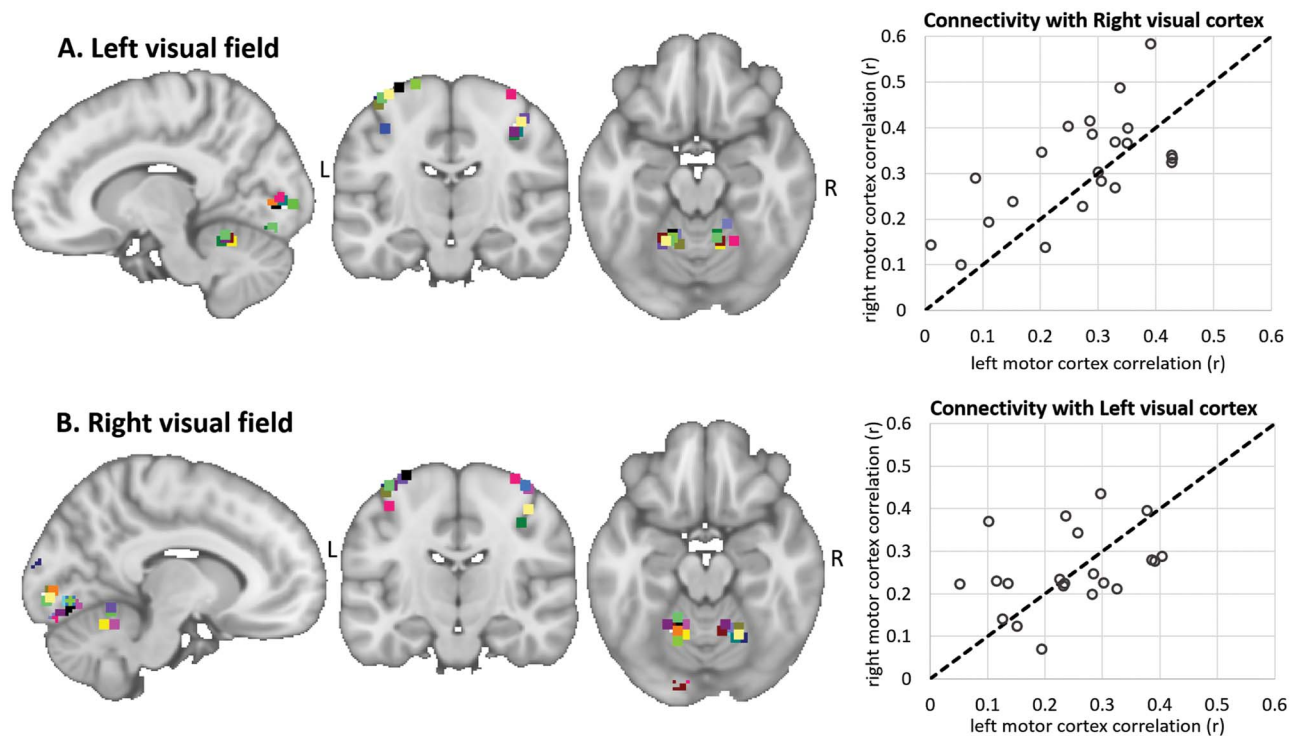
Figure 4. Functional connectivity between visual cortex and motor cortex. Functional connectivity between stimulated visual cortex and right/left motor cortices during task execution. Visual, motor, and cerebellar ROIs of individual subjects ($N = 22$) presented on sagittal, coronal, and axial views of an MNI template (left panels; each color represents a 27 voxels ROI of an individual subject; see Methods). Panel A corresponds to left visual field runs and Panel B to right visual field runs. Scatter plots to the right display the functional connectivity (Pearson's r) between right (top) or left (bottom) visual cortex and the two motor cortices. Each dot represents data of a single subject, and dashed line indicates equal functional connectivity with right/left motor cortices. During left visual field runs (Panel A), right visual cortex exhibited stronger functional connectivity with right versus left motor cortex ($t = 2.29$, $P < 0.05$), but during right visual field runs (Panel B), no significant difference was found ($t = 0.81$, $P = 0.43$). R—right hemisphere, L—left hemisphere.

visual field. Our fMRI results show that despite identical physical properties of the visual stimulus, neural activity in visual cortex differentiated the stimulus-triggering hand. Finally, functional connectivity analysis between visual cortex and ipsilateral/contralateral motor cortex and cerebellum showed stronger connectivity between right visual cortex and the ipsilateral (right) motor cortex and no difference in connectivity strength with right/left cerebellum. For left visual cortex, no differences in functional connectivity were found.

Results from our MVPA analysis show that activation patterns in visual cortex to identical visual stimuli are different, depending on the stimulus-triggering hand. In other words, actions that generate visual feedback are associated with responses in visual cortex that are sensitive not only to the visual properties of the stimulus but also to the hand that was used to generate it. This nonintuitive result suggests that efference copies contain information not only regarding the expected sensory outcome but also about the effector that triggered it. This is in agreement with an emerging line of evidence demonstrating limb-specific neural modulations. Recent EEG evidence shows differential magnitudes of sensory attenuation (expressed in the evoked response signal) for stimuli generated with various effectors (e.g., the hand, eyes, or mouth) in the visual (Mifsud et al. 2018) and auditory (Mifsud et al. 2016) modalities. In addition, previous fMRI studies report differential signals in visual regions when the same effector is used to

perform different actions (Chapman et al. 2011; Gallivan et al. 2015; Gutteling et al. 2015).

In a recent fMRI study, Gallivan et al. (2019) had participants prepare and execute grasping and reaching movements toward a target object, with their right or left hand. Using MVPA, they report differential response patterns in visual cortex during execution of similar actions performed with the right/left hand. These results support hand-specific modulations in visual cortex. However, it is important to note that since participants saw their hands, the visual input during right/left-hand execution trials was not identical and may potentially explain differential activity in visual cortex. Additionally, the modulations in visual cortex may also be ascribed to visual feedback related to online motor control. In our current study, participants did not see their hands and the visual consequences of their actions (gray circle) were identical across conditions. Thus, our current results provide further evidence for effector-specific modulations and demonstrate that such modulations occur also in the absence of online visual feedback necessary for motor control. Interestingly, in previous studies, significant hand-specific modulations were also reported during the action preparation phase (i.e., before actual movement; Gallivan et al. 2019, see also Gallivan et al. 2013). Importantly, with respect to efference copies and coding of expected sensory consequences, the use of left/right-hand results in different expected sensory outcomes. In our current study, we kept expected sensory outcome

identical for the two hands, yet we could still distinguish between stimuli triggered with the right/left hand. However, due to the experimental design we used, we cannot determine whether such differences begin already in the preparation phase of the action.

Another interesting aspect of our results is that despite presenting visual stimuli in one visual field in a given experimental condition, we found that limb-dependent modulations were not restricted to the visual cortex contralateral to the stimulated visual field. Instead, we find significant modulations also in ipsilateral visual cortices. One interpretation of this finding is that button presses modulate signals in visual cortex in a global, nonspecific manner, including visual regions in the ipsilateral hemisphere that are not engaged by the stimulus. An alternative explanation is that button presses modulate evoked responses that are present also in ipsilateral visual cortex. Although it is common to associate visual stimulation in one visual field with activations in the contralateral visual cortex (Gilbert 2013), previous studies have shown activations also in the visual cortex ipsilateral to the stimulated visual field (Tootell et al. 1998; Smith et al. 2004b). Therefore, the hand-dependent modulations we report in both visual cortices may still reflect specificity of the motor signals to visual regions sensitive to the visual stimulus. Indeed, in the current experiment, we found significant ipsilateral activations during the localizer runs; however, in the experimental runs, we failed to find such activations at the group level. This could be due to lower salience of the visual stimulus used (gray circle vs. checkerboard) or poor alignment of weak ipsilateral activations across participants. Finally, previous studies report motor modulations in visual cortex that are specific to task-relevant areas (as assessed by retinotopic mappings) (Gallivan et al. 2013, 2019; Gutteling et al. 2015). Taken together, it is likely that the significant hand-decoding voxels we find in visual cortex ipsilateral to the stimulated visual field respond to the stimulus and are modulated by specific motor signals.

Related to this point, it is not clear at this stage whether the modulations we report in visual cortex are due to the causal link between the button presses and the visual consequences. Since the aim of the current study was to explore the dependency of sensory modulations on limb identity, we did not manipulate the causal link, for example, by measuring neural responses in visual cortex during right/left button presses with no visual consequences. To the best of our knowledge, no previous study reported limb-specific modulations of visual cortex in the absence of visual stimulation. The forward model framework would suggest that the expectancy of sensory consequences plays an important role in sensory modulations. Therefore, under this framework, in the lack of expected visual consequences, differential hand-dependent modulations in visual cortex should not be found. Whether limb-specific modulations in visual cortex can be found in the absence of visual stimulation is an interesting question for a future study.

While it is assumed that the efference copies originate from the motor system, as proposed by the forward model (Wolpert et al. 1995; Crapse and Sommer 2008), the anatomical origin of such signals is not known. Although our current data do not unequivocally resolve this issue, our results are in better agreement with a neuroanatomical source that exhibits a laterality bias. In this respect, some studies suggest that efference copies originate from the active motor cortex (Gandolla et al. 2014; Reznik et al. 2014), while others suggest the cerebellum to be the origin of these signals (Blakemore et al. 2001; Person 2019; Kilteni and Ehrsson 2020). By manipulating the hands used to generate

the stimulus, and the stimulated visual field, we engaged different motor and visual pathways across experimental conditions. Therefore, to the extent that active motor pathways are the source of sensory modulations, it is plausible for modulations in sensory cortex to reflect their different motor origins. Our functional connectivity data demonstrate that right visual cortex is more strongly connected with the right (vs. left) motor cortex, while functional connectivity with right/left cerebellum was not significantly different. In the left visual cortex, we found no significant differences in functional connectivity with either right/left motor cortex or right/left cerebellum suggesting possible hemispheric differences in connectivity. While these results are in better agreement with a cortical source of modulations, it is important to note that the hemodynamic response function as measured by the MR scanner is different between the cerebral cortex and the cerebellum (Hossein-Zadeh et al. 2003; Chen and Desmond 2005), a fact that may potentially bias functional connectivity analysis in favor of cortical regions (visual/motor) over cortex-cerebellum connectivity. A recent study using a tactile paradigm points to functional connectivity between somatosensory cortex and contralateral cerebellum (Kilteni and Ehrsson 2020). Regardless of the source (cerebellar/cerebral), our results are in better agreement with neuroanatomical regions exhibiting differential signals for right/left hand.

A large body of literature reporting sensory modulations in humans has focused on the auditory and tactile modalities (Blakemore et al. 1999; Baess et al. 2009; Lange 2011; Weiss et al. 2011; Reznik et al. 2015a), with fewer studies characterizing this phenomenon in the visual domain (Cardoso-Leite et al. 2010; Straube et al. 2017; Yon and Press 2017; Csifcsak et al. 2019). Thus, our behavioral results provide an expansion of the current literature in the visual domain with respect to stimulus brightness. Moreover, to the best of our knowledge, there is no previous evidence demonstrating effector-dependent sensory modulations at the behavioral level. A common finding in previous behavioral results, irrespective of sensory modality, is the attenuation of reported perceptual intensity (e.g., tactile pressure or sound amplitude; Blakemore et al. 1999; Reznik et al. 2015a). In our current results, the direction of perceptual modulations was not consistent across participants, with some reporting increased stimulus brightness and others reporting decreased stimulus brightness of the self-generated stimuli. Nevertheless, when comparing the magnitude of modulations across hands, we found stronger modulations when the stimulus-triggering hand and stimulated visual field are ipsilateral and thus predominantly processed in the same hemisphere. We recently proposed a model in which sensory regions are more strongly modulated when the motor region engaged in producing the action resides in the same hemisphere (Reznik et al. 2014). The behavioral and neural results of the current study are in agreement with such a model.

There is an ongoing discussion regarding the functional role of efference copies and sensory modulations, including agency attribution, and desensitization of sensory apparatus (Gentsch and Schutz-Bosbach 2011; Burin et al. 2017; Haggard 2017). Although our study does not address these functional roles, our results suggest that to the extent that sensory modulations are involved in such processes, they should have a component of limb specificity. Additionally, it should be noted that to date, there is no direct causal evidence linking the behavioral and physiological phenomena of sensory modulations, and many studies report either one. Although in the current study we report both measures from the same participants, differences

in design and analysis levels precluded us from performing a direct comparison of measures across participants.

In motor cortex, recent evidence from EEG demonstrates differences in readiness potential that depend on the coupling with a sensory consequence (Reznik et al. 2018). Thus, together with the current results, it seems that information about expected sensory consequences is stored in the motor cortex, while limb-specific motor information of signal source is stored in the sensory cortex (visual cortex in the current study). Although speculative at this point, such modulations both in motor and sensory cortices may constitute an important neural loop for sensorimotor learning. In summary, by demonstrating limb-specific sensory modulations both at the behavioral and neural levels, our results help constrain future models describing their underlying mechanisms and provide further evidence that neural responses in regions primarily described by their sensory properties (in our case "visual cortex") go beyond a simple representation of the physical/optical properties of the external world.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Notes

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