

Pulvinar Response Profiles and Connectivity Patterns to Object Domains

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Distributed cortical regions show differential responses to visual objects belonging to different domains varying by animacy (e.g., animals vs tools), yet it remains unclear whether this is an organization principle also applying to the subcortical structures. Combining multiple fMRI activation experiments (two main experiments and six validation datasets; 12 females and 9 males in the main Experiment 1; 10 females and 10 males in the main Experiment 2), resting-state functional connectivity, and task-based dynamic causal modeling analysis in human subjects, we found that visual processing of images of animals and tools elicited different patterns of response in the pulvinar, with robust left lateralization for tools, and distinct, bilateral (with rightward tendency) clusters for animals. Such domain-preferring activity distribution in the pulvinar was associated with the magnitude with which the voxels were intrinsically connected with the corresponding domain-preferring regions in the cortex. The pulvinar-to-right-amygdala path showed a one-way shortcut supporting the perception of animals, and the modulation connection from pulvinar to parietal showed an advantage to the perception of tools. These results incorporate the subcortical regions into the object processing network and highlight that domain organization appears to be an overarching principle across various processing stages in the brain.

Key words: animal domain network; domain selectivity; pulvinar; subcortical; tool domain network

Significance Statement

Viewing objects belonging to different domains elicited different cortical regions, but whether the domain organization applied to the subcortical structures (e.g., pulvinar) was unknown. Multiple fMRI activation experiments revealed that object pictures belonging to different domains elicited differential patterns of response in the pulvinar, with robust left lateralization for tool pictures, and distinct, bilateral (with rightward tendency) clusters for animals. Combining the resting-state functional connectivity and dynamic causal modeling analysis on task-based fMRI data, we found domain-preferring activity distribution in the pulvinar aligned with that in cortical regions. These results highlight the need for coherent visual theories that explain the mechanisms underlying the domain organization across various processing stages.

Received Mar. 28, 2022; revised Nov. 30, 2022; accepted Dec. 10, 2022.

Author contributions: H.W. and X.W. performed research; H.W. and X.W. analyzed data; H.W., Y.S., M.L., P.Z., X.W., and Y.B. wrote the paper; X.W. and Y.B. designed research.

This work was supported by National Science and Technology Innovation 2030 Major Program 2021ZD0204104 to Y.B.; National Natural Science Foundation of China 32071050 to X.W. and 31925020 and 82021004 to Y.B.; and 81971694 to M.L.; Changjiang Scholar Professorship Award T2016031 to Y.B.; and Fundamental Research Funds for the Central Universities 2021NTST11 to X.W. The Human Connectome Project data were provided by the WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657), which is funded by the 16 National Institutes of Health Institutes and Centers that support the National Institutes of Health Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. We thank the investigative teams providing the publicly available dataset and the funding agencies that made these datasets available; Ke Wang, Yaya Jiang, Xinyu liang, Shijia Fan, Ze Fu, Guoli Lv, and Siyuan Zhou for constructive suggestions in data analysis; and Prof. Wu Li for helpful comments.

The authors declare no competing financial interests.

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<https://doi.org/10.1523/JNEUROSCI.0613-22.2022>

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Introduction

One of the broad principles of visual object processing in the human cortex is domain structure. Viewing several domains of objects, including animals, small manipulable objects (tools), and large nonmanipulable objects, has been found to elicit different patterns of response in distributed cortical regions, including and beyond the ventral temporal cortex, which has been explained by their association with evolutionary-salient functions, such as fight-or-flight (animals) or manipulation (tools) (He et al., 2013; Konkle and Caramazza, 2013; Garcea and Buxbaum, 2019; Schone et al., 2021; Wen et al., 2022; for review, see Bi et al., 2016; Peelen and Downing, 2017). Viewing tools elicits activation in a left-lateralized cortical network, including the left lateral occipitotemporal cortex, the inferior and superior parietal lobule, and the medial fusiform gyrus, which have been

proposed to process various properties of tools that support its shape, use, and function (Brandi et al., 2014; Fabbri et al., 2016; Chen et al., 2018; Wang et al., 2018). Viewing animals elicits activation in the bilateral/right lateral fusiform (and amygdala), which is assumed to reflect visual and emotional properties associated with animals (Mormann et al., 2011; J. Yang et al., 2012; Bi et al., 2016). While the functionality of these domain-preferring cortical regions has been extensively studied, the potential roles of subcortical regions that are richly connected with the cortex remain poorly understood.

Among the visual-related subcortical areas (Saalmann and Kastner, 2011; Bridge et al., 2016; Fiebelkorn and Kastner, 2019; Jaramillo et al., 2019; Guedj and Vuilleumier, 2020), pulvinar, the largest nucleus in the primate thalamus, has shown particularly intriguing selectivity patterns for certain types of visual stimuli. Functional imaging, lesion, and animal evidence have indicated that the pulvinar is sensitive to salient visual objects, including threatening faces (Ward et al., 2007; Koizumi et al., 2019; McFadyen et al., 2019, 2020) and animals (i.e., snake) (Le et al., 2013, 2016). Sensitivity to nonthreatening faces has also been reported in the pulvinar (Nguyen et al., 2016; McFadyen et al., 2017; Arcaro et al., 2018). Based on indirect evidence, it has been speculated that the pulvinar may also be involved in tool processing. Pulvinar lesion leads to deficits in reaching and grasp (Wilke et al., 2018), which were closely related to tool use. When V1 is blocked, dorsal cortical areas still showed robust activation to images of tools, which has been assumed to be achieved through direct subcortical projections to the dorsal cortical pathway (Fang and He, 2005). Arcaro et al. (2018) corroborated this speculation by showing that cortical tool regions were intrinsically functionally connected with the dorsal pulvinar. However, systematic investigations of whether and how the pulvinar processes visual stimuli with a domain pattern, and its relationship with the cortical domain distribution, are lacking.

To examine whether object domain organization is also present in the pulvinar, forming a cortical-subcortical domain network, we tested the pulvinar response patterns and cortical connectivity patterns associated with different domains of objects, focusing on animals and tools given the previous empirical observations about their potential sensitivity in the pulvinar. Conspecific neutral faces and large nonmanipulable manmade objects were included as reference conditions to depict the relative domain specificity. We focused on the pulvinar because of the previous clues of its sensitivity to various specific animate items, and because its size allows investigation using the current 3T fMRI resolution without compromising the whole-brain scan to understand the cortical-subcortical connectivity pattern. We combined fMRI activation experiments, resting-state connectivity analyses, and task-based dynamic causal modeling (DCM) to address the following questions: (1) whether the pulvinar shows significant, consistent activity patterns specifically associated with animals or tools relative to other objects; (2) if any potential animal and/or tool domain preferring activity patterns are discovered within the pulvinar, whether it is functionally connected with corresponding domain-preferring cortical regions, forming a domain-specific functional network; and (3) what the direction of information flow is within the pulvinar-cortical domain-preferring systems during visual processing.

Materials and Methods

3.5 mm

animals being less smooth and more textured (smoothness, animal vs large nonmanipulable object/tool, p values < 0.001 , animal vs face, $p = 0.16$; texturedness, all p values < 0.001) and tools being more elongated and having smaller pixel number ratio (elongation, pixel number ratio, all p values < 0.001). Results will be considered in light of such property differences.

Experimental design. In Experiment 1, fMRI data were acquired when subjects viewed pictures from the four object domains over four block-design runs (Fig. 1A). Each run lasted for 300 s, began and ended with a 10 s fixation period, during which a fixation was presented at the center of the screen. Each run consisted of 12 task blocks (three for each

object domain), separated by 8 s intervals of a blank screen. Each block presented 20 pictures from a single object domain, and each picture was presented for 600 ms, with an interstimulus interval of 200 ms. The subjects were instructed to look at the pictures carefully and to press a button with the 294.9(t)m1msndex finger as soon as they detected a picture that appeared twice in a row (one-back task). Within each block, the planned number of button presses was 0, 1, or 2. The total number planned button presses was matched across object domains and runs. The presentation order of pictures in each block was random 294.9(t)8(z)0(e)17.9(d)14.4(.), presented for 300s,th an interstiulus interval of 500.n Experiment subjects took an 8-min-long (240 vlumes) resting-state fMRI scan before task-fMRI scanning, during which the subjects were asked to close the 294.9-3.6(r)-227.4(ey).6(es)-231.4(a).7(n)1.9(d)-230.5 Imaging Center for Bra.9-3.6(n)-304.9(R)2.6(e)-6.7(s)2(e)0(a)-6(r)-7(c)-2(h)2.3(.)-303.7(TE = 30 ms, flip angle (FA) $\times 90^\circ$, matrix size = $643 \times$

³ with gap of 0.7 mm). Hig-resolution 3D T1-weighted iages were acquired using the-MPRAGE sequenc (144 sagittal slices, TR = 2530 ms, TE = 3.39 ms, FA = 7° , matrix 2-408.2(s).4(i)1.4(z)0(e)-168.4(=)-1

size = 224×256 , interpolated to 448×512 , slice thickness = 1.0 mm, voxel size = $0.5 \times 0.5 \times 1 \text{ mm}^3$).

Data preprocessing. Task fMRI data were preprocessed using Statistical Parametric Mapping software (SPM12; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). No subject exhibited excessive head motion in either experiment ($>3 \text{ mm}$ maximum translation or 3° rotation in Experiment 1 and $>2 \text{ mm}/2^\circ$ in Experiment 2). After the first five volumes of each functional run were discarded for signal equilibrium, the functional data underwent slice timing, head motion correction, and normalization into the MNI space using unified segmentation. The resulting functional images with isotropic voxels (3 mm for Experiment 1; 2 mm for Experiment 2) were further spatially smoothed with a 4 mm FWHM Gaussian kernel.

Resting-state fMRI data were preprocessed using SPM12, the toolbox for Data Processing & Analysis for Brain Imaging (version 5.1) (Yan et al., 2016) and analyzed using the resting-state fMRI Data Analysis Toolkit version 1.8 (Song et al., 2011). No subject exhibited excessive head motion ($>2 \text{ mm}$ maximum translation or 2° rotation). For each subject, preprocessing follows conventional procedures, which include the following: (1) discarding the first 5 volumes for signal equilibrium; (2) slice timing; (3) correcting for head movement; (4) regressing out nuisance variables, including the global signal averaged across the whole brain, mean white matter (WM), the CSF signals, and continuous head movement (Friston-24 parameters) (Friston et al., 1996) to further reduce non-neuronal signal confounds; (5) removing the signal trend with time linearly; (6) bandpass (0.01-0.1 Hz) filtering; (7) normalization into MNI space by DARTEL (Ashburner, 2007); and (8) spatial smoothing with a 4 mm FWHM Gaussian kernel.

Data analysis

For each individual subject, the preprocessed task-functional images were entered into a GLM. For each run, the GLM included four regressors of interest corresponding to the four object domains, each convolved with the canonical HRF. The GLM also included six head motion parameters as regressors of no interest. The high-pass filter was set at

We also analyzed data from the WU-Minn HCP (<https://www.humanconnectome.org/study/hcp-young-adult>; approved by the Institutional Ethics Committee of Washington University, St. Louis, Missouri) (Van Essen et al., 2013). For the current analyses, we used the fMRI data of the working memory task, which included stimuli from four object domains (i.e., faces, places, tools, and body parts) (Barch et al., 2013). We used the minimally preprocessed images (for detailed preprocessing procedure, see Glasser et al., 2013), which were further spatially smoothed with a 4 mm FWHM Gaussian kernel. Other data processing (i.e., constructing a GLM, contrasting object domains, and conducting the group analyses) was the same as that of Experiments 1 and 2. We did not differentiate between the task conditions (i.e., 0-back, 2-back) that the working memory experiment included. A total of 910 subjects were identified, as they did not exhibit excessive head motion (>2 mm maximum translation or 2° rotation) or any data quality issues, as reported in the HCP project manual (https://www.humanconnectome.org/storage/app/media/documentation/s1200/HCP_S1200_Release_Reference_Manual.pdf). The analysis was confined to the individuals who were right-handed (handedness index > 40 , $N = 786$) (Arshad et al., 2013). Tool activation was not localized in four individuals, and the remaining 782 subjects entered the individual analysis. We also validated our results on 392 individuals (discarding those that were in the sibling cohorts) to further rule out the intersubject dependence caused by genetic similarity.

Resting fMRI connection analysis. We tested the communication between the pulvinar and cortical object domain regions using the object picture viewing fMRI data from Experiment 1, and the resting-state fMRI data collected from an independent group of 144 right-handed healthy young subjects (described by H. Yang et al., 2017). All subjects gave written informed consent to the experimental protocols, which were approved by the Institutional Review Board of the National Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University. The scan lasted for 6 min and 40 s, during which the subjects were asked to close their eyes and to not fall asleep. The preprocessing steps included the removal of the first 10 volumes, slice timing, motion correction, spatial normalization into MNI space using unified segmentation (resampling voxel size was $3 \times 3 \times 3$ mm³), linear trend removal, bandpass filtering (0.01–0.1 Hz), spatial smoothing (6 mm FWHM Gaussian kernel), and regression of nuisance variables (including six rigid head motion parameters, the global signal, the white matter signal, and the CSF signal). Given the controversy regarding the global signal regression (Liu et al., 2017; Murphy and Fox, 2017), we also performed the analysis without regressing out global signal.

We first identified cortical regions showing significant domain selectivity by contrasting each object domain with the average of the other three domains in the whole brain in Experiment 1. For each object domain, all cortical regions that survived the threshold of voxel-level $p < 0.001$, one-tailed, cluster-level family-wise error (FWE)-corrected $p < 0.05$ were collectively defined as the corresponding domain-selective “cortical seed ROI” (Fig. 4A). The overlapping voxels between cortical regions from different domains and the overlapping clusters between cortical regions and pulvinar were excluded from the subsequent analysis. As Figure 4A shows, mean time series were calculated by averaging the time series extracted from all voxels in each corresponding domain-selective “cortical seed ROI” for each subject in the independent resting fMRI data ($N = 144$). For each object domain, a cortico-pulvinar connectivity map was generated by correlating the time series of the corresponding domain cortical seed and the time series of each pulvinar voxel, while regressing out the time series from the other three object domain cortical seeds. The resulting r maps were further Fisher-transformed and tested against zero across subjects. The resulting t maps were defined as domain-specific cortico-pulvinar RSFC maps and were further correlated with the object domain activation maps in Experiment 1 (t map, each specific object domain vs the average of the other three object domains) to examine whether the cortico-pulvinar RSFC pattern corresponded to the object domain activation pattern. To statistically test the domain specificity of the RSFC-activation correspondence, we compare the within versus between domain correlations: correlations between the animal cortico-pulvinar RSFC map and the animal domain activation map versus

correlations between the animal cortico-pulvinar RSFC map and the other three object domain activation maps and correlations between the animal object domain activation map and the other three object domain-specific cortico-pulvinar RSFC maps, using the Hotelling’s t test (the FZT computator, <http://psych.unl.edu/psycrs/statpage/regression.html>). Comparisons for tools were computed in the same manner.

We also collected the RSFC data of subjects in Experiment 2, and thus performed this analysis (task fMRI and RSFC relationship) using RSFC and fMRI activation data from the same group of subjects. The procedure was the same except that to include the frequently reported fusiform face area when viewing neutral face images, we defined the face-selective cortical seed under a more lenient threshold (voxel-level $p < 0.01$, one-tailed, cluster-level FWE-corrected $p < 0.05$).

DCM analysis

To determine the direction of information flow across the pulvinar-cortical domain-preferring systems, we performed DCM analysis using DCM12 (Friston et al., 2003) in the SPM12 software. DCM analysis allows us to investigate the direction of information flow between the pulvinar and cortical domain regions, and most importantly explore whether and how certain object domain modulates the directional connection (Penny et al., 2010; Stephan et al., 2010; Zeidman et al., 2019a, b). DCM is a hypothesis-driven technique. Models with different hypotheses of neural connectivity are constructed at the beginning, and then tested using Bayesian Model Selection (BMS) to decide which model or which family of models provides the most likely explanation of the observed data.

In the present study, we focused on how processing animals and tools stimuli modulated the intrinsic connectivity between the pulvinar and the corresponding cortical domain clusters. We were especially interested in whether the directional connections between pulvinar and cortical domain clusters were modulated by corresponding object domain. Based on our interest and for the sake of simplicity, we constructed models with only three ROIs: the pulvinar, primary visual cortex (V1), and object domain cortical ROIs. Different object domain cortical ROIs were tested separately, with only one ROI tested at a time. The external perturbation (all the four object domains) entered our model through both the pulvinar and V1. We considered all possible combinations of connections between the object domain cortical ROI and the pulvinar, and between the object domain cortical ROI and the visual primary cortex (Fig. 5A, no connection, only forward connection, only backward connection, or both forward and backward connections, combined with only intrinsic connection or object domain modulation connection), giving us a comprehensive model space of 80 models (models having no connection between either two regions were deleted). No intrinsic connection was defined between the pulvinar and V1 (McFadyen et al., 2019, 2020). The experiment input was mean-centered, which means that the intrinsic connection represented the average effective connectivity across object domain conditions and modulation connection was added to or subtracted from this average (Zeidman et al., 2019a). The model was estimated for each run for each subject. As we focused on the pulvinar-cortical communication, we further grouped our models into 9 families (Fig. 5A, Family A to Family I) according to the presence of intrinsic connections and modulation between the pulvinar and cortical clusters. The DCM analyses were conducted on Experiment 2 data with higher spatial resolution to ensure the inclusion of an adequate number of voxels.

For the tool domain, a left-lateralized cortical tool network was defined by contrasting tools with the average of the other three object domains (voxel-level $p < 0.001$, cluster-level $p < 0.05$, FWE-corrected), including ROIs in the lateral occipitotemporal cortex (LOTc, peak MNI coordinates: $-46, -66, -4$), the medial fusiform gyrus (FG, peak MNI coordinates: $-26, -64, -16$), and the superior parietal lobe (SPL, peak MNI coordinates: $-38, -46, 60$). Left V1 (peak MNI coordinates: $-14, -100, 0$) was defined by contrasting all object domain conditions versus resting baseline within the Brodmann mask (area 17) (Maldjian et al., 2003) restricted to the left hemisphere. For these areas, we defined the group ROI by placing spheres with a radius of 8 mm around corresponding peak coordinates. For the pulvinar, we used the predefined left

pulvinar mask as the group ROI. We then searched for the peak tool-selective activations (i.e., tool vs the average of other three domains) within the group ROIs in each individual subject. One subject was excluded because no voxel survived the height threshold of uncorrected $p < 0.05$. Single-subject ROIs were then constructed as spheres (radius = 3 mm, 19 voxels) centered on each subject's peak coordinates. A BOLD time series was obtained for each subject, and each ROI using the voxels that survived the uncorrected $p < 0.05$ in single-subject ROIs.

For the animal network, to include more animal-related areas (e.g., left FG), we defined animal ROIs using the contrast between animals versus large nonmanipulable object and tool conditions (voxel $p < 0.001$, FWE-corrected $p < 0.05$). We found selective activation to animals outside the bilateral pulvinar in the bilateral lateral occipital cortex (LO, MNI coordinates: left LO, $-48, -80, 6$; right LO, $50, -74, 0$) and the bilateral FG (MNI coordinates: left FG, $-42, -50, -24$; right FG, $40, -48, -20$). Using the all-object domain conditions versus resting baseline contrast combined with the Brodmann mask (area 17), we defined the left V1 and right V1 (MNI coordinates: left V1, $-14, -100, 0$; right V1, $26, -96, 10$). For these areas, we defined the group ROI by placing spheres with a radius of 8 mm around these coordinates. As previous studies found that both the left and right amygdala responded to animals (both threatening and neutral animals) (Mormann et al., 2011; J. Yang et al., 2012), together with the evidence that the amygdala interacted with the pulvinar (Pessoa and Adolphs, 2010), we also included the amygdala as ROIs using the anatomic AAL mask (Amygdala_L, AAL 41; Amygdala_R, AAL 42) (Tzourio-Mazoyer et al., 2002). For the pulvinar, we used the pulvinar mask we described previously. We then searched for the individual peak coordinates within the group ROIs using the animal versus large nonmanipulable manmade objects and tool contrast. The procedures of discarding subjects and extracting time series were the same as those of the tool network analyses. For analyses of left OC and left FG, 3 subjects were discarded because no voxel survived the threshold of voxel $p < 0.05$, uncorrected in the left pulvinar, while for analyses of the right OC and right FG, 1 subject was discarded because no voxel survived the threshold of voxel $p < 0.05$ of the right pulvinar. For analyses of the left amygdala and right amygdala, 1 subject was discarded from each, as no voxel survived the extent threshold of voxel $p < 0.05$ of itself.

The previously described nine model families, representing nine competing hypotheses, were compared using random effect BMS. When comparing model families, all models within a family were averaged using Bayesian Model Averaging, and an exceedance probability was calculated for each family. The winning family was defined as the one with the highest exceedance probability. In the present study, as our interest was the relationship between the pulvinar and the cortex (or the amygdala), BMS was first performed on the nine model families with different pulvinar-cortical communication types (Fig. 5). BMS performed on the 80 models, choosing the best model, were also conducted for validation.

Data and materials availability

The data that support the findings of this study are available at https://osf.io/6cgex/?view_only=7788e2dd7ee6442599461113af5f486b.

Results

The following three lines of results were reported: (1) To test whether the pulvinar showed significant, consistent sensitivity pattern associated with animals and/or tools, two fMRI picture viewing experiments were performed. The observed domain sensitivity pattern was validated using five in-house, previously collected datasets, and using the HCP dataset. (2) To test the relationship between cortical and pulvinar animal/tool preference distributions, the cortico-pulvinar RSFC map was computed, and its relationship with pulvinar domain activation pattern was examined. (3) To test the direction of information flow within the pulvinar-cortical network for each domain (i.e., among the pulvinar and cortical domain-preferring clusters), the DCM analysis was conducted on the task-state fMRI data.

Object domain-preferring activity topography in the pulvinar

Two object domain experiments with identical stimuli, with varying design and scanning parameters, were conducted for

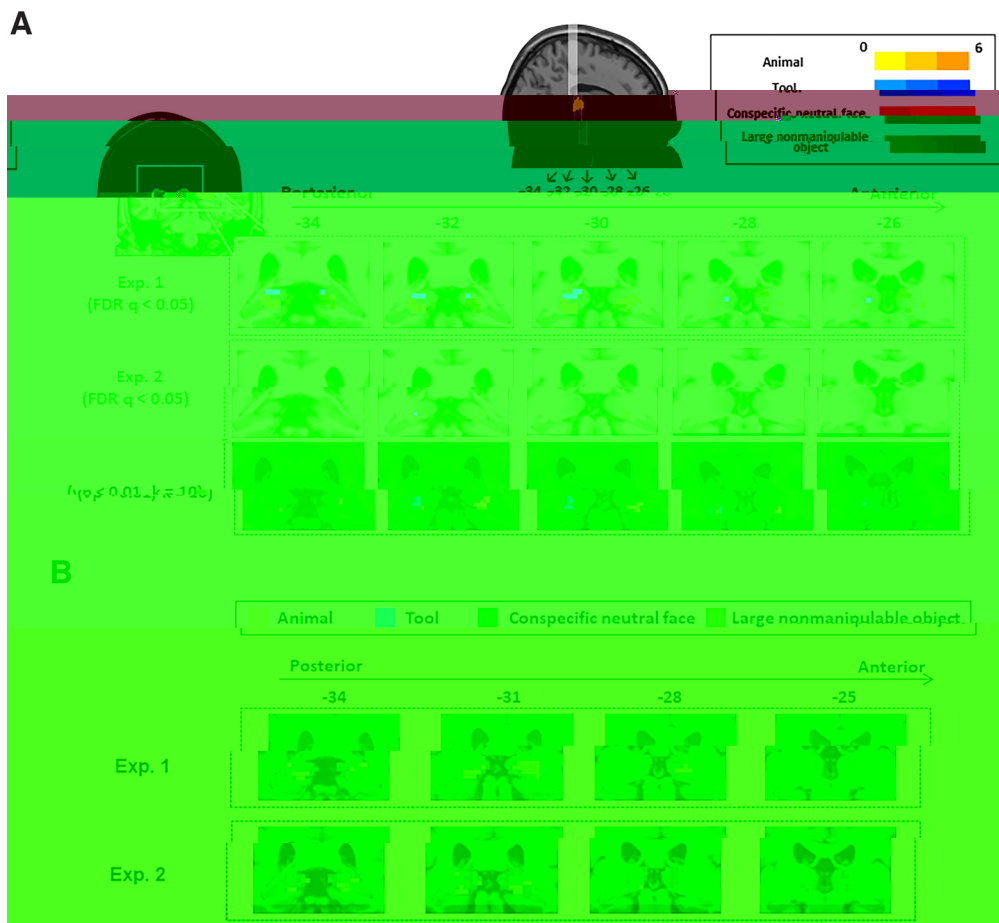


Figure 2. Object domain-prefering activity topography in the pulvinar. **A**, Object domain-prefering activity topography in the pulvinar. The pulvinar mask (yellow) was presented in coronal (top left) and sagittal (top middle) slice views. The thresholded activation pattern of the pulvinar is shown in coronal views from posterior to anterior with MNI y coordinates denoted. Color bars in the top right inbox represent the *t* values of the domain preference contrast (each domain vs the average of the other three). Experiment 1 (3 mm³ resolution) and Experiment 2 (2 mm³ resolution) are shown in the top and bottom panels, respectively. **B**, Winner-take-all maps in the pulvinar in Experiments 1 and 2. Color of each voxel represents the domain that induces the highest activation across all domains in the corresponding voxel. The maps are presented in the same resolution (3 mm³) for visual comparison.

Table 2. Object domain preference results for the pulvinar in Experiments 1 and 2

				MNI coordinates		
	Object domains	Peak voxel (<i>T</i> value)	Cluster size (voxels)	<i>x</i>	<i>y</i>	<i>z</i>
Experiment 1 (FDR voxel <i>p</i> < 0.05, confined to the pulvinar)	Animal vs others	4.38	18	−21	−30	0
		3.49	10	18	−30	3
	Face vs others	5.48	11	12	−33	0
		3.25	1	−9	−33	0
		3.21	6	6	−27	9
	Large nonmanipulable object vs others	2.34	1	−21	−27	3
	Tool vs others	3.87	9	−18	−33	6
		2.47	1	12	−33	6
Experiment 2 (FDR voxel <i>p</i> < 0.05, confined to the pulvinar)	Animal vs others	5.30	8	18	−30	−2
	Face vs others	—	—	—		
	Large nonmanipulable object vs others	—	—	—		
	Tool vs others	3.91	1	−20	−32	2
Experiment 2 (voxel <i>p</i> < 0.01, <i>k</i> > 10)	Animal vs others	5.30	25	18	−30	−2
		3.08	2	−16	−34	−2
		2.54	1	−18	−28	0
	Face vs others	—	—	—		
	Large nonmanipulable object vs others	—	—	—		
	Tool vs others	3.91	15	−20	−32	2
		3.32	3	−16	−26	2

domain preference statistical maps across two experiments (animal $r = 0.32$, $p < 0.001$; tool $r = 0.28$, $p < 0.001$) were significantly larger than between-domain correlations across experiments (for animals: p values < 0.01 ; for tools: p values < 0.001 , except $p = 0.11$ for within tools vs between large objects-tools).

Reference object domain results

For the two reference object domains (conspicuous neutral faces and large objects), the large objects induced negligible pulvinar responses compared with other object domains in both experiments (Fig. 2A). The neutral face preference was inconsistent between experiments. In Experiment 1, face-preferring voxels were observed predominantly in the medial part of the right pulvinar (Fig. 2A; Table 2, $\chi^2 = 14.22$, $p < 0.001$, $df = 1$). In Experiment 2, no voxel showed above-threshold preference for conspicuous neutral faces even under the most lenient threshold of voxel $p < 0.01$, $k = 10$. Looking at the winner-take-all maps for the two experiments, there was a consistent right-hemisphere preference for neutral faces (Fig. 2B, Experiment 1: right pulvinar, $n = 28$, left pulvinar, $n = 10$, $\chi^2 = 8.53$, $p = 0.004$, $df = 1$; Experiment 2: right pulvinar, $n = 125$, left pulvinar, $n = 45$, $\chi^2 = 37.65$, $p < 0.001$, $df = 1$). In the analyses below, we focused on the animal and tool domains given their robust activation results and the theoretical interest explained in the Introduction.

LI results: robust laterality of object domain preference in the pulvinar

In the analyses above, we consistently observed that the tool-preferring voxels tended to be found in the left hemisphere, while the animal-preferring voxels tended to be more bilaterally distributed (Experiment 1) or right-lateralized (Experiment 2). Here, we quantify this observation by computing the LI for each domain using the LI toolbox (Wilke and Lidzba, 2007) implemented in SPM12 (for details, see Materials and Methods). The LIs were computed based on the t maps of each object domain versus the average of the other three object domains at both the group level and the individual level. The LI varies between the range from -1 to 1 , with -1 being completely right-lateralized, 1 being completely left-lateralized, and values between -0.2 and 0.2 considered as bilateral (Seghier, 2008; for a more lenient cutoff of laterality [$|LI| > 0.1$], see Szaflarski et al., 2006).

Group lateralization results

Consistent with the object domain preference and winner-take-all maps, the pulvinar showed strong left laterality of tool-preferring voxels at the group level in both experiments (Experiment 1: 0.83; Experiment 2: 0.61). The animal-preferring voxels in the pulvinar were evenly distributed between the hemispheres in Experiment 1 and were right-lateralized in Experiment 2 (Experiment 1: 0.05; Experiment 2: -0.26).

Individual lateralization results

We further tested whether the object domain preference lateralization was reliable at the individual subject level. For each object domain, one-sample t tests were conducted against zero on the LIs computed from the t maps of individual subjects. As shown in Fig. 2, the results revealed significantly left-lateralized tool preference (Fig. 3B, Experiment 1: mean LI = 0.25, $t = 3.11$, $p = 0.005$, $df = 20$, Cohen's $d = 0.68$; Experiment 2: mean LI = 0.20, $t = 2.74$, $p = 0.013$, $df = 19$, Cohen's $d = 0.61$) across subjects in both experiments. There was no significantly lateralized animal preference in either Experiment 1 (Fig. 3B, Experiment 1: mean LI = -0.04 , $t = -0.49$, $p = 0.63$, $df = 20$) or Experiment 2

(mean LI = -0.03 , $t = -0.46$, $p = 0.65$, $df = 19$). Individual LIs are also presented in the bar plot in Figure 3B. Together, across the two experiments of differing spatial resolution, we observed relatively consistent left-lateralized tool preference in the pulvinar across individual subjects, while no clear, consistent laterality effects were observed for animals across subjects.

Validation of the lateralization effects in the pulvinar across multiple datasets

In both Experiments 1 and 2, lateralization was the most consistent and salient functional specialization pattern for different object domains in the pulvinar. To further validate this effect, we reanalyzed the data of five previously conducted experiments from our laboratory (of which four were published) that included picture viewing of animals and/or tools (He et al., 2013; Wang et al., 2016, 2017, 2018; Wu et al., 2020; Fan et al., 2021), yet did not scrutinize the pulvinar effects at the time. In four of the five experiments, tools showed left lateralization in pulvinar in the group analysis (Fig. 3C, LI: VD1, 0.91; VD2, 0.41; VD3, 0.66; VD4, 0.49). The VD5 (LI: 0.13) also showed a left lateralization trend in a more lenient cutoff of laterality ($|LI| > 0.1$, Szaflarski et al., 2006). The animals showed a right preference in three of the four validation datasets (VD3 did not contain animals; Fig. 3C, LI: VD1, 0.28; VD2, -0.42 ; VD4, -0.36 ; VD5, -0.59). The left lateralization of animals in VD1 was caused by the strong right lateralization of faces in this dataset. When excluding the face category, animals (vs the average of large objects and tools) still showed a right lateralization (LI = -0.2). Pooling all subjects together (115 individuals for tools and 96 for animals), one-sample t tests showed that the pulvinar showed left lateralization for tools (Fig. 3C, $t = 3.27$, two-tailed $p = 0.001$, $df = 114$, Cohen's $d = 0.30$) and a right preference for animals (Fig. 3C, $t = -2.31$, two-tailed $p = 0.02$, $df = 95$, Cohen's $d = -0.24$). We also analyzed data from the HCP dataset (subject $N = 782$) (Van Essen et al., 2013). This dataset included a picture viewing task with four object domains including a "tool" condition (although not all typical tools as investigated in our experiments), faces, scenes and body parts, but did not contain animals. A strong left lateralization for tools was again found in the group results (LI = 0.41). The effects were also highly robust in the individual analyses (Fig. 3C, $t = 3.79$, two-tailed $p < 0.001$, $df = 781$, Cohen's $d = 0.14$). These results held when we excluded genetically related individuals (who were twins or non-twin siblings) (remaining $N = 392$; $t = 2.76$, two-tailed $p = 0.006$, $df = 391$, Cohen's $d = 0.14$).

RSFC results: the cortico-pulvinar RSFC pattern aligns with the animal and tool domain pulvinar activation pattern

Now that we have observed domain-sensitive patterns in the pulvinar for tools and animals, do they associate with the corresponding domain preference clusters in the cortex? We used an independent resting-state fMRI dataset ($N = 144$) (H. Yang et al., 2017) to test the intrinsic functional connectivity pattern between the pulvinar and cortex.

We first defined cortical regions showing significant preference for the corresponding domain in Experiment 1 as the "cortical seed network" (Fig. 4A, vs the average of the other three object domains, voxel-level $p < 0.001$, one-tailed, cluster-level FWE-corrected $p < 0.05$). Animal cortical seed network included left and right lateral fusiform and occipital areas. Tool cortical seed network included LOTC, parietal, medial fusiform, and occipital areas. We then computed the Pearson correlation between the mean time series of each cortical seed network (i.e.,

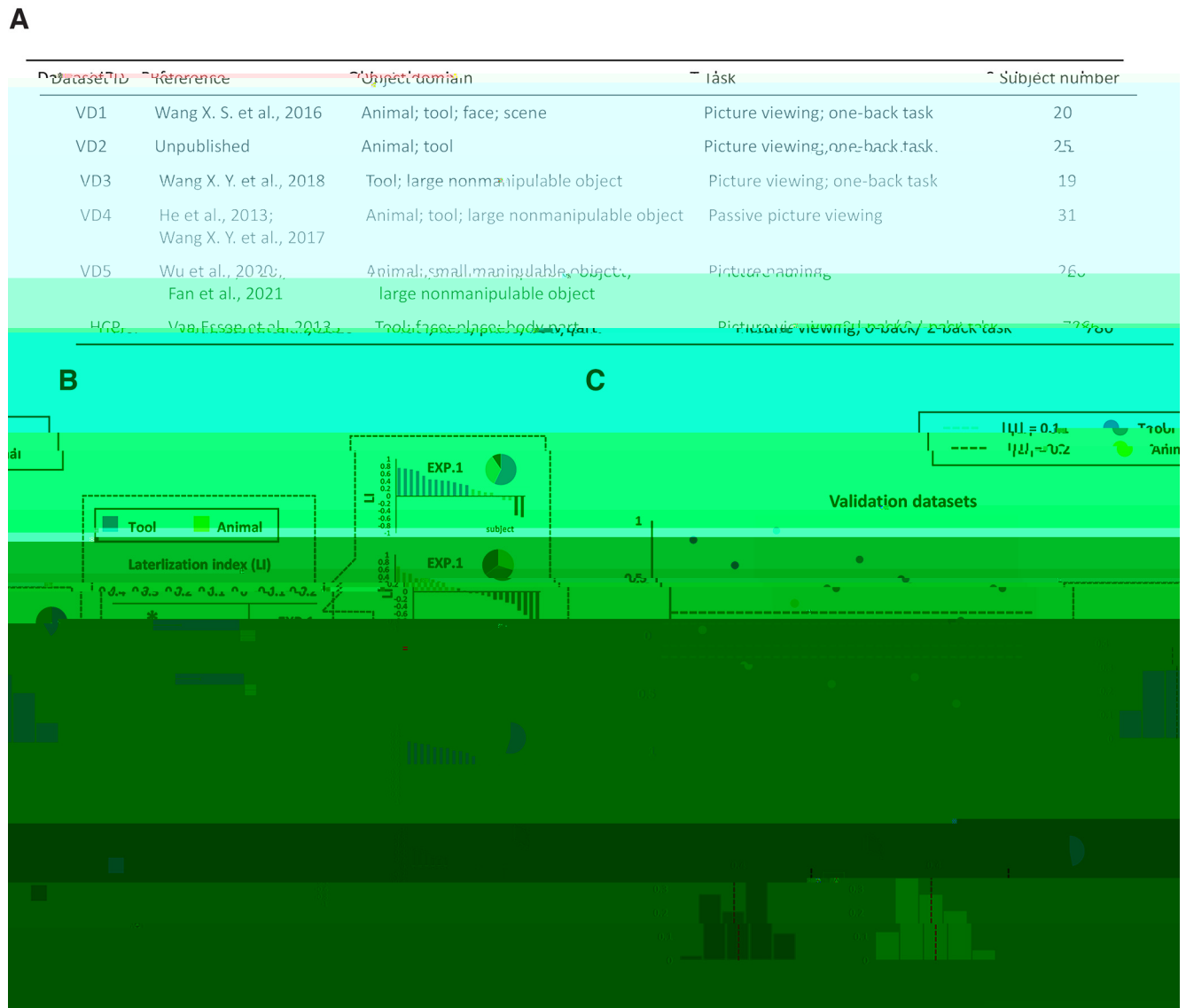


Figure 3. Robust laterality of object domain preferences in the pulvinar. **A**, Summary of validation datasets. **B**, Laterlization in the pulvinar at the individual level. Bar plots represent the LI for animals and tools in the pulvinar. Asterisks were shown when the LIs of the animal or tool conditions across individuals are significantly higher than zero. Error bars indicate SEs. Individual LIs for animals and tools are further shown on the right side, with the pie chart showing the population proportion of laterlization preference ($|LI| > 0.2$). The subjects are sorted according to their LI index for each object domain condition in each experiment. **C**, Laterlization in the pulvinar at the group level. The animal and tool group LIs for Experiment 1, Experiment 2, the validation datasets, and the HCP dataset are shown. The frequency distribution diagrams of individual LIs for Vd 1–5, and HCP data set are shown, with the pie chart showing the population proportion of laterlization preference ($|LI| > 0.2$).

time series averaged across all voxels within each cortical seed network) and the time series of each voxel in the pulvinar, while regressing out the mean time series of the other three object domain cortical seed networks, creating a cortico-pulvinar RSFC map for each object domain (Fig. 4A; see Materials and Methods).

The r values in each pulvinar voxel of each cortico-pulvinar RSFC map reflected how strongly that voxel connected with cortical clusters showing preference for the corresponding domain. To quantify whether the pulvinar voxels' domain preference (reported in the above sections) was aligned with the their RSFC with specific object domain cortical seed network, we correlated the cortico-pulvinar RSFC maps with the pulvinar domain activation maps (t maps, each object domain vs the average of the other three object domains). As shown in Figure 4B, the within-domain correlations between the RSFC map and the domain activation map were highly significant for animals and tools (animal: $r = 0.56$, $p < 0.001$; tool: $r = 0.26$, $p < 0.001$; the left-most

bars in each plot). That is, the more strongly a pulvinar voxel was intrinsically synchronized with animal cortical network, the more strongly it was activated by animal pictures relative to other domains, and the same pattern held for tools.

These RSFC-activation alignments were domain-specific as the cross-domain correlations were significantly lower than the within-domain correlations (Fig. 4B, shaded bars; for animals: Hottelling's t values > 3.3 , $P_{s_{corrected}} < 0.01$; for tools: Hottelling's t values > 3.0 , $P_{s_{corrected}} < 0.05$; $df = 167$, two-tailed, Bonferroni-corrected). The cross-domain correlations were computed by correlating the pulvinar domain activation map with RSFC-pulvinar maps with one map from the concerning interested domain (i.e., animal or tool) and the other map from the other three object domains.

Given the controversy regarding the removal of global signals in RSFC analyses, we further conducted the computation without regressing out the global signal, and the results held (for

[illegible]

Figure 4. The cortico-pulvinar RSFC pattern aligns with the animal and tool domain pulvinar activation patterns. **A**, Cortical ROIs for RSFC analysis and cortical-pulvinar RSFC map creation. Top, The ROIs defined for each object domain (vs the average of the other three object domains, voxel-level $p < 0.001$, one-tailed, cluster-level FWE-corrected $p < 0.05$) using Experiment 1. Bottom, A schematic overview of the cortico-pulvinar RSFC map creation. **B**, Correlations between cortico-pulvinar RSFC maps and pulvinar domain activation maps using Experiment 1 and an independent RSFC dataset ($N = 144$). Bar graphs represent correlations between animal (or tool) cortico-pulvinar RSFC map and animal (or tool) domain activation map (the leftmost bar), correlations between animal (or tool) activation map and other three object domain cortico-pulvinar RSFC maps (bars with horizontal lines), and correlations between animal (or tool) cortico-pulvinar RSFC map and other three object domain activation maps (bars with oblique lines). Solid black line indicates that Hotelling's t test between the two r values found they were significantly different ($p_{corrected} < 0.05$, $df = 167$, two-tailed, Bonferroni correction time = 6). Scatter plots represent the correlations between the animal (tool) cortico-pulvinar RSFC map and the pulvinar animal (tool)

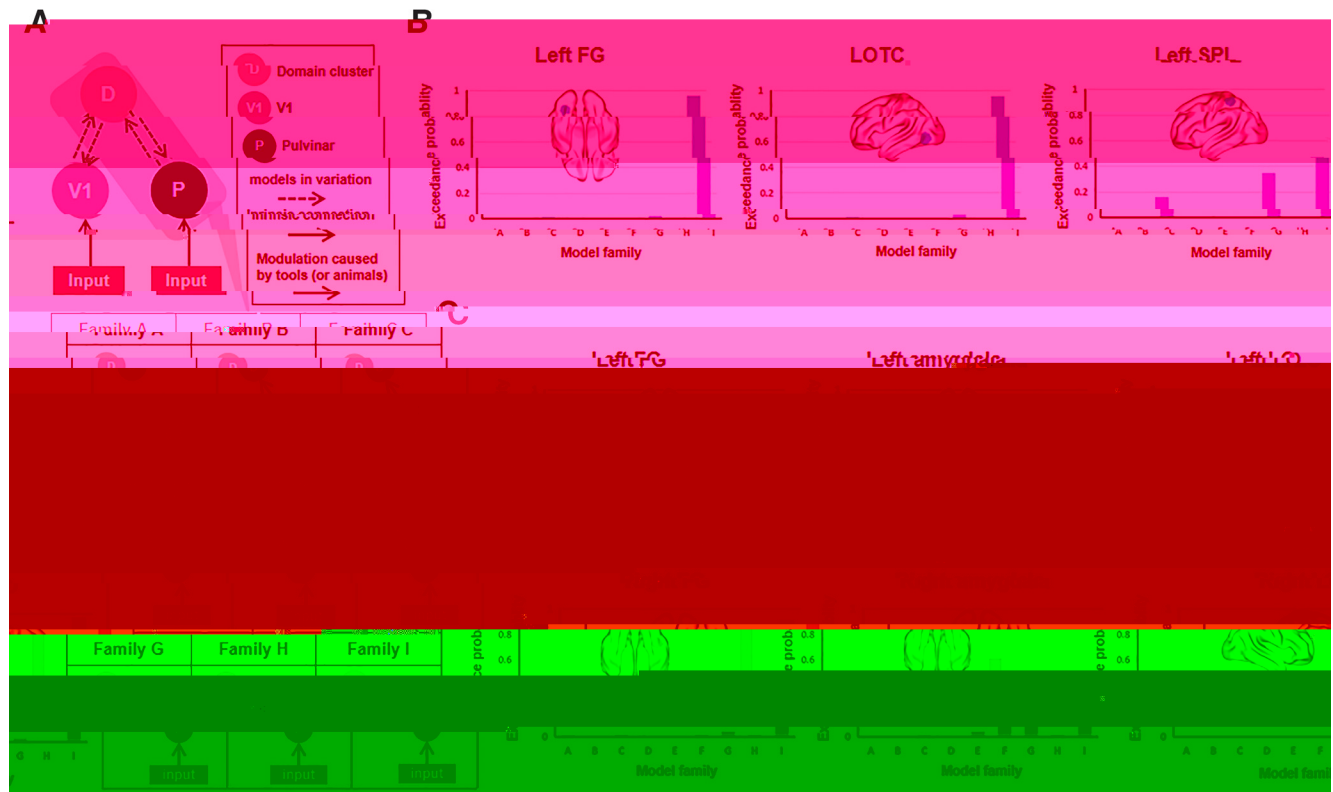


Figure 5. DCM analysis results. **A**, Structure of DCM models. Top, The basic model structure. The primary visual cortex (V1), tool, or animal domain cortical (or amygdala) ROI and the pulvinar were chosen to constitute the model. The dotted arrows can be set as no connection, only intrinsic connection, and modulation caused by tools or animals. All the possible combinations of connections gave us a comprehensive model space of 80 models. Nine families were defined to partition the whole model space with no overlap, as shown in the bottom panel. **B**, Exceedance probabilities of each family for tool domain ROIs. The tool ROIs are shown in the corresponding position of the diagram. **C**, Exceedance probabilities of each family for animal domain ROIs. The animal ROIs are shown in the corresponding position of the diagram.

animals: within-domain $r = 0.58$, between-domain mean $r = -0.06$, within- vs between-domain, Hotelling's t values > 4.3 , $P_{\text{corrected}} < 0.001$; for tools: within-domain $r = 0.29$, between-domain mean $r = -0.16$, within- vs between-domain, Hotelling's t values > 3.2 , $P_{\text{corrected}} < 0.01$; $df = 167$). Using the HCP RSFC data preprocessed in Wen et al. (2022), the results again showed strong alignment between the RSFC pattern and the functional activation pattern in pulvinar (for animals: within-domain $r = 0.43$, between-domain mean $r = 0.03$, within- vs between-domain, Hotelling's t values > 2.9 , $P_{\text{corrected}} < 0.05$; for tools: within-domain $r = 0.17$, between-domain mean $r = -0.09$, within- vs between-domain, Hotelling's t values > 2.8 , $P_{\text{corrected}} < 0.05$; $df = 592$). We also tested our results with Experiment 2, where the functional activation data and the resting-state fMRI data were collected from the same group of subjects. The results showed a similar pattern (Fig. 4C).

DCM analysis results

Having established that the pulvinar has domain-differentiating response topology for tool and animal domains and that it is intrinsically connected with the corresponding domain-preferring clusters in the cortex, forming domain-specific pulvinar-cortical

networks, we next examined the direction of the information flow. We used DCM to address this question (Fig. 5A). Data from Experiment 2 were used given its relatively high spatial resolution ($2 \times 2 \times 2 \text{ mm}^3$).

Model ROI definition

ROIs for the tool models and animal models included cortical regions showing tool or animal preferences, the pulvinar, and primary visual cortex. Cortical domain ROIs were obtained by drawing a sphere with an 8 mm radius centered on the peak coordinate of the domain contrast from Experiment 2 (shown in Fig. 5B,C; voxel-level $p < 0.001$, one-tailed, cluster-level FWE-corrected $p < 0.05$). Tool ROIs included the LOTC, superior parietal lobule, and FG, and we focused on the left hemisphere clusters given the strong lateralization (see above). Animal ROIs (animal vs tools and large objects) included bilateral LO and bilateral FG. We additionally included the anatomically defined bilateral amygdala (AAL template: Amygdala_L, AAL 41; Amygdala_R, AAL 42) as animal ROIs, given that it has been reported to show a preference for animals (Mormann et al., 2011; J. Yang et al., 2012) and has connections with the pulvinar (Pessoa and Adolphs, 2010). The primary visual cortex, defined as the visually activated voxels (i.e., all object domains vs rest baseline) within the Brodmann area 17, was included because of its essential role in visual processing.

Families set

The basic model structure included an object domain cortical ROI, the pulvinar, and the primary visual cortex. We considered

←

activation map. Each dot represents a voxel in the pulvinar. **C**, Replication using Experiment 2. The ROIs were defined using Experiment 2. All object domain activation maps and object domain cortical-pulvinar RSFC maps were obtained from Experiment 2. Solid black line indicates that Hotelling's t test between the two r values found they were significantly different ($p_{\text{corrected}} < 0.05$, $df = 592$, two-tailed, Bonferroni correction time = 6).

all possible combinations of connections (no connection, only forward connection, only backward connection, or both forward and backward connections, combined with only intrinsic connection or object domain modulation connection) between the object domain cortical ROI and the pulvinar, and between the object domain cortical ROI and the primary visual cortex, giving us a comprehensive model space of 80 models. No connection was set between the pulvinar and the primary visual cortex (McFadyen et al., 2019, 2020). We focused on information flow between the pulvinar and cortical domain-preferring clusters, defining 9 families (Fig. 5A, Family A to Family I) that partitioned the whole model space into different families with no overlap. BMS was then used to compare these competing families that represented different hypotheses.

Tool results

For all the tool cortical ROIs, the best family was Family I (Fig. 5B, exceedance probability: LOTC, 0.96; left FFG, 0.96; left SPL, 0.47): bidirectional intrinsic connection and bidirectional tool-specific modulation between the pulvinar and the cortical clusters. This indicated that tool information flowed both from the pulvinar to the tool cortical clusters and from the tool cortical clusters to the pulvinar. Notably, for the left SPL, the second-best family was Family G (exceedance probability: 0.35), and the third best was Family C (exceedance probability: 0.16), which only contained forward tool modulation from the pulvinar to the SPL, indicating an essential role for forward modulation. The best model for all the tool cortical ROIs belonged to the best family, and the second and third best model for SPL also belonged to the second and third best family for SPL, respectively, which was consistent with the current best family results.

Animal results

For all the animal cortical ROIs, the best family was Family I, which contained bidirectional intrinsic connections and bidirectional animal modulations (Fig. 5C, exceedance probability: left FG, 0.50; right FG, 0.91; left LO, 0.91; right LO, 0.97), indicating the bidirectional nature of animal preference patterns in the pulvinar and cortex. For the left amygdala, the winning family was Family F (Fig. 5C, exceedance probability: 0.38), which contained only intrinsic connections between the left pulvinar and the left amygdala without any animal modulation; for the right amygdala, Family G was the winning one (Fig. 5C, exceedance probability: 0.62), which only contained animal modulation from the right pulvinar to the right amygdala. This pulvinar-amygdala right lateralization of modulation was consistent with the trend of the right lateralization observed in the local activity analyses reported above. The results using the best model were consistent with these best family results.

Discussion

Across two main experiments and multiple validation datasets (five in-house ones), we found robust, consistent tool-specific left lateralization effects in the pulvinar. Viewing pictures of tools, compared with other objects, consistently elicited stronger activation in the left pulvinar. Clusters specific to animals were also observed in the pulvinar, distributed bilaterally with a right lateralization trend. The domain selectivity strength for tools and for animals across pulvinar voxels was associated with how strongly the voxel was intrinsically connected with the cortical clusters showing the corresponding domain preference. DCM revealed that, during visual processing, the pulvinar communicated with cortical domain areas in a bidirectional fashion, with

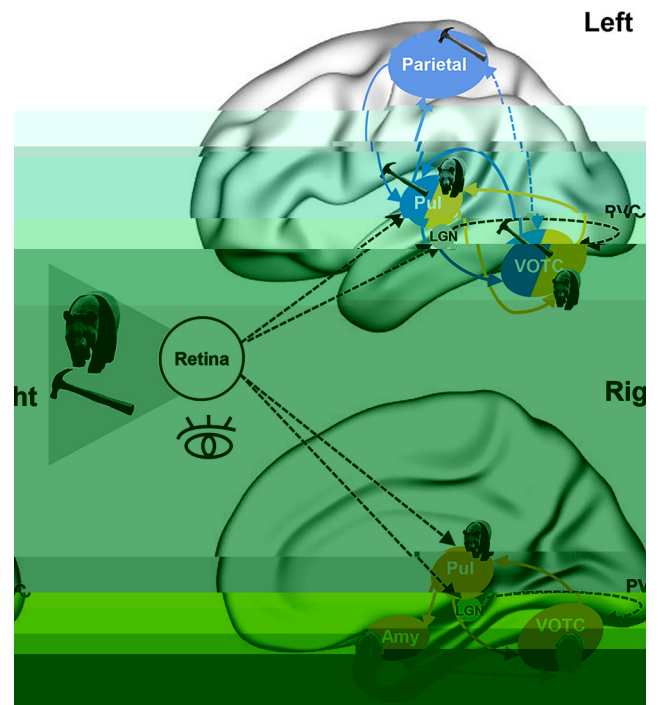


Figure 6. Summary of pulvinar-cortical domain preference systems. The left hemisphere and right hemisphere are shown (Xia et al., 2013) in the top and bottom panels, respectively. The brain regions are shown in the approximate areas. Arrow indicates the direction of information flow. Solid line indicates the modulation found in our study. Dashed lines indicate the path found (or speculated) by previous articles. Yellow represents modulation or activation by animal images. Blue represents modulation or activation by tool images. The LGN-PVC-VOTC pathway has been described by many previous articles (e.g., Grill-Spector and Weiner, 2014).

modulation from the pulvinar to the superior parietal regions showing a more unique role during tool-viewing and to the right amygdala during animal-viewing (Fig. 6).

Our observation that the pulvinar contains clusters showing stronger activity to animals than other types of visual objects corresponds with findings from macaques, which observed pulvinar neurons' selectivity to threatening animate objects, such as snakes (Le et al., 2013, 2016). Interestingly, we also observed the modulation effect from the pulvinar to the right amygdala, which has also been shown to respond more strongly to animals (J. Yang et al., 2012). It has been proposed that the direct connection between pulvinar and amygdala constituted the shortcut for emotion and threatening information (Pessoa and Adolphs, 2010; McFadyen et al., 2020). In line with this proposal, animal stimuli in our experiments were indeed rated to be more threatening and of higher arousal than other objects. Thus, the pulvinar-amygdala animal-preferring pathway may support the fast fight-or-flight responses to (threatening) animals. The animal-preferring pulvinar voxels also tend to be more strongly functionally connected (bidirectional links) with cortical areas showing animal preference (e.g., bilateral FG and LO). That is, the pulvinar contains animal-preferring clusters that link with previously reported animal-preferring cortical clusters and the amygdala in a larger loop, and modulates the amygdala's response to animals, potentially serving as the gateway for animal perception.

The most robust finding of domain specificity was a preference for tool pictures in the left pulvinar. This is a highly robust left lateralization effect consistently observed across 8 datasets (i.e., two main experiments, 5 in-house validation datasets, and the HCP dataset) and across contrasts. Such left lateralization of the pulvinar is aligned with cortical left lateralization effects for tools, and voxel-wise tool preference patterns in the pulvinar were associated with the intrinsic connectivity pattern with the cortical tool-preferring clusters (LOTc, SPL, and medial FG), consistent with the observation that the tool cortical regions were functionally coupled with part of the pulvinar, based on resting-fMRI analyses (Arcaro et al., 2018). Such observations provide further positive evidence of the pulvinar's role in giving rise to tool selectivity, which has been speculated based on indirect evidence (Fang and He, 2005; Wilke et al., 2018). While the DCM results supported bidirectional connections among these regions, it is worth noting that the model with modulation only from the pulvinar to the parietal clusters also had a higher exceedance probability. That is, tool selectivity in the left pulvinar might be more than mere peripheral feedback activation from left-lateralized tool cortical network but rather an integral constituent of a left-lateralized cortical-subcortical network for tool processing.

The origin and functionality of lateralization in the human brain are controversial, with some proposing that lateralization increases processing efficiency (Rogers et al., 2004; Vallortigara, 2006; Corballis, 2017). Regarding tools, the left brain lateralization is observed in humans and often discussed relating to the right-handedness (e.g., Lewis, 2006). Intriguingly, Cheng et al. (2021) examined white matter structural connectivity patterns across species and showed that macaques and humans differed significantly in the lateralization effect in the IPL, a region that has been consistently implicated in tool processing in humans. Humans showed leftward asymmetric connectivity between the IPL and regions, including the primary motor cortex, ventral premotor cortex, SPL, and posterior MTG, but macaques showed no significant leftward asymmetric connections. Our present results showed that such left hemispheric advantage for tools is not only a cortical signature but also robustly manifested in subcortical structures; the relationship between such tentative human-specific brain patterns for tools and human-specific complex tool use behavior (Gibson et al., 1994; Vaesen, 2012) requires further investigation.

More generally, how do the observations of pulvinar response and connectivity patterns contribute to theories about visual object processing in the brain? What information about tools and animals is being processed in the pulvinar? Traditional object domain processing theory primarily focuses on cortical processing, where low-level, retinotopic visual information processed in V1 is organized into higher-level visual and nonvisual representations downstream that give rise to the animacy domain structure observed later on, without explicit assumptions about the functionality of subcortical structures (e.g., Grill-Spector and Weiner, 2014). A related proposal emphasizes that the domain structure also partly reflects an organization that is driven by the perception-response loop, the way that the brain processes sensory signals is constrained by how optimally they map onto responses for survival (Mahon and Caramazza, 2011; Peelen and Downing, 2017; Bi, 2020; Fan et al., 2021). This notion predicts that the evolutionarily salient domain structures cut across all stages of the perception-response system, even in subcortical structures, manifested along with the intrinsic properties of each stage. In our experiments on the pulvinar, we matched different domains of images on low-level

visual image properties, including mean luminance, contrast, color (all grayscale images), and spatial frequency; thus, the pulvinar selectivity patterns were not simply driven by such information. Nonetheless, animal and tool pictures still tend to differ along other higher-level visual information, such as shape, size, and texture, with tools being more elongated in shape, having smaller (real-world) size, smoother, aligning with the existing literature (Konkle and Caramazza, 2013; Chen et al., 2018; Long et al., 2018). These sensory signals are also differently associated with many other types of nonvisual information that varies across domains, including the types of responses, such as fight-or-flight (for animals) and grasping, manipulation, and functional use (for tools). Whether the object domain effects observed in the cortical regions are reducible to some specific or combinations of these properties are still under debate (e.g., Grill-Spector and Weiner, 2014; Nasr et al., 2014; Bryan et al., 2016; Fabbri et al., 2016; Proklova et al., 2016; Bracci et al., 2019; Yue et al., 2020; Fan et al., 2021). Along the same line, what exactly pulvinar processes to give rise to the observed domain sensitivity and connectivity patterns, and potentially other subcortical structures, such as LGN and SC, remain to be vigorously tested with specific hypotheses and finer measurements.

A few open issues need to be considered. Arcaro et al. (2018) reported face preferences in the medial pulvinar. While we also observed such an effect in Experiment 1, we only found right lateralization of face preferences without any voxels surviving correction in Experiment 2. Compared with the other object categories, the face category comprises items of greater homogeneity (subordinates), which may introduce stronger repetition suppression effects. The robustness of the face effects in pulvinar thus remain to be further examined. Second, for the DCM analysis, we did not test the fully possible range of connections among all regions (cortical and subcortical) but focused on the information flow between the pulvinar and other regions. Choosing all regions and connections at a time may give a more comprehensive understanding, but also results in a huge computational burden and make the model too complex. Finally, we only examined the (resting-state and task) functional connectivity of pulvinar in the current study and did not have structural connectivity data on the same subjects. The relationship between structural and functional connectivity is a general question of the brain research (e.g., see discussions in Honey et al., 2009). The few studies on pulvinar have reported general alignment: Arcaro et al. (2015) reported, in both RSFC and diffusion-weighted imaging data, the ventral pulvinar were more strongly connected with early and associative visual cortex whereas the dorsal pulvinar with frontoparietal regions. McFadyen et al. (2019) reported a subcortical structural pathway from superior colliculus via pulvinar to amygdala underlying the recognition of fearful faces. The more comprehensive structural subcortical-cortical pathway underlying the functional domain network remain to be further charted, and the current functional connectivity results guide such investigations.

In conclusion, we have shown that visual processing of different domains of objects (animals and tools) triggers different patterns of response in the pulvinar, with robust left lateralization for tool pictures and distinct, bilateral (rightward) clusters for animals, which aligns with domain-specific cortical (and amygdala) activation patterns through intrinsic and task-based functional connectivity. While the pulvinar and cortical domain-specific clusters overall show bidirectionality, the pulvinar-to-right-amygdala path shows a one-way shortcut supporting the perception of animals; the modulation connection from the pulvinar to superior parietal

cortex shows an advantage in the perception of tools. These results incorporate subcortical regions, especially the pulvinar, into the object processing network and highlight the need for coherent visual theories that explain the mechanisms underlying domain-appearing-organization across various processing stages.

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