Title1: Wire together, function together: Base connectivity explains category-specific activation and impairment

Title2: Wire together, function together: Architectural constraints of cortical semantic network

**Authors:** Lang Chen1,3\*, Matthew A. Lambon Ralph2, Timothy T. Rogers1

**Affiliations:**

1Department of Psychology, University of Wisconsin-Madison, 1202 West Johnson Street, Madison, WI 53705, USA

2Neuroscience and Aphasia Research Unit (NARU), School of Psychological Sciences, University of Manchester, UK

3Stanford Cognitive and Systems Neuroscience Laboratory, 1070 Arastradero Rd. Suite 220, Palo Alto, CA 94304, USA

\*Correspondence to: Lang Chen (halleycl@gmail.com)

**Abstract**: Research on understanding neural representations of conceptual knowledge in human brain has for long focused on distinct patterns of functional brain activations for different semantic categories, e.g., animals and manmade objects, in healthy population and selective impairments to these categories in brain-damaged patients. We present converging evidence from brain data and model simulations to propose a novel perspective explaining why and how category-specific activation and impairment emerge. Brain regions showing preferential activations to either animal or manmade concepts were identified by meta-analysis, and further shown to interconnect with each other within a distributed network by a probabilistic tractography analysis of white-matter tracts. A neuro-computational network adopting the same architecture was then shown to account for both category-specific activation and impairments. These results indicate that the organization of neural representations in cortical semantic network is constrained by both initially-specified connectivity and learning.

**One Sentence Summary:** Patterns of brain activation and selective impairment to different semantic categories depends on the architecture and learning environment of cortical semantic network.

**Main Text:**

How cortical semantic network is organized in human brain has been long in the focus of cognitive and neuroscientific research ([Haxby et al., 2001](#_ENREF_25); [Martin, Wiggs, Ungerleider, & Haxby, 1996](#_ENREF_39)). This question underlines the fundamental discrepancy between two prominent theories of semantic knowledge: one (the domain-specific view) argues that semantic categories (e.g., animals, fruit/vegetables, manmade objects, faces, etc.) function as the first-order constraint to the network architecture (i.e., specific connectivity between brain regions)([Mahon & Caramazza, 2009](#_ENREF_31)) and they are processed separately by discrete neural correlates ([Caramazza & Shelton, 1998](#_ENREF_10); [Kanwisher, 2010](#_ENREF_27)), whereas the other (the domain-general view) claims that different semantic categories are represented and processed within the same cortical network in a widely distributed manner ([McClelland & Rogers, 2003](#_ENREF_41); [Patterson, Nestor, & Rogers, 2007](#_ENREF_46); [Rogers et al., 2004](#_ENREF_51)). The importance of this question also signifies by the wide range of approaches researchers have taken. Since the seminal report of category-specific impairment by Warrington and her colleagues ([Warrington & McCarthy, 1983](#_ENREF_57)), many single-case studies on brain-damaged patients have examined that selective semantic impairment can occur to categories such as animals, manmade objects, fruits/vegetables ([Laiacona, Capitani, & Caramazza, 2003](#_ENREF_28)), seemingly supporting the domain-specific view. By contrast, the domain-general view can well account for the overall degeneration of semantic knowledge to all categories (category-general) observed in patients with semantic dementia (SD), a progressive disorder affecting anterior temporal lobe (ATL), usually bilaterally, especially in the lateral and ventral aspect ([Adlam et al., 2006](#_ENREF_3); [Hodges, Patterson, Oxbury, & Funnell, 1992](#_ENREF_26)). In recent arena of functional neuroimaging, some studies demonstrated that differential functional activation can be induced for different semantic categories in normal population ([Chao & Martin, 2000](#_ENREF_12); [Mahon et al., 2007](#_ENREF_34); [Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995](#_ENREF_37)) and even in individuals with unusual sensory experiences ([Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009](#_ENREF_30); [Mahon, Schwarzbach, & Caramazza, 2010](#_ENREF_35)). Researchers embracing the domain-general views also have endeavored great efforts on computational models to understand the interactive nature of the distributed semantic network and how different patterns of semantic impairments, both category-specific and category-general, emerge from the same network ([Lambon Ralph, Lowe, & Rogers, 2007](#_ENREF_29); [Plaut, 2002](#_ENREF_47); [Plaut & Behrmann, 2011](#_ENREF_48); [Rogers et al., 2004](#_ENREF_51)).

Unfortunately, however, current research falls short of adjudicating between different theoretical views as well as providing a unified framework to integrate different research approaches. In neuropsychological research, the category-specific impairment observed in many, if not all, patients may be overestimated because items from different semantic categories vary in many confounding factors, such as their familiarity or frequency in language, their reliance on different perceptual and functional properties, and the covariance structure of their visual and/or semantic properties ([for a review, see Chen & Rogers, 2014](#_ENREF_13)). At the meanwhile, besides category-general impairment observed in SD patients, category-selective impairments are indeed reported reliably in three neuropathological groups: patients with Herpes Simplex Virus Encephalitis (HSVE) showing animal-related impairment ([Lambon Ralph et al., 2007](#_ENREF_29); [Noppeney et al., 2007](#_ENREF_44)), patients with temporal tumors showing impairments to manmade objects ([Campanella, D’Agostini, Skrap, & Shallice, 2010](#_ENREF_9)), and patients with pure alexia showing loss of knowledge about living things ([Behrmann & Plaut, 2012](#_ENREF_5)) (other ref?). Similarly, the category-sensitive activation can be actually epiphenomenal— in posterior fusiform gyrus, differential activation pattern for animals and manmade objects was driven by confounding factors like visual similarity ([Rogers, Hocking, Mechelli, Patterson, & Price, 2005](#_ENREF_50)), feature salience ([Mechelli, Sartori, Orlandi, & Price, 2006](#_ENREF_43)), and expertise ([Gauthier, Skudlarski, Gore, & Anderson, 2000](#_ENREF_21)), but reliable activation patterns for different categories were well documented in regions including pFG, posterior middle temporal gyrus (pMTG), and inferior parietal lobule (IPL) and so on ([Chouinard & Goodale, 2010](#_ENREF_14)). For previous computational models, despite their success in accounting for some patterns of semantic impairment like in SD patients, little is done to investigate whether a single model for semantic knowledge can account for category-sensitive activations in neuroimaging studies in addition to a wide spectrum of category-general and category-specific impairment patterns. Therefore, different views of semantic knowledge are difficult to reconcile based on existing evidence, and we lack for a model framework that can accommodate findings from different research approaches.

Here, we present a series of studies combining functional and structural neuroimaging evidence as well as model simulation results to (a) test a different hypothesis, the “base-connectivity hypothesis” which not only bridges two contrasting theoretical views, but also attempts to answer pressing questions why and how category-specificity in brain activation and impairments emerges from a neural network through learning the environmental structures embedded in semantic categories; and (b) to provide a general methodological framework of how neuroimaging and computational models can mutually inform each other in order to understand neurocognitive networks. The “base-connectivity” hypothesis starts with the basic tenet of many domain-general views that cross-modal semantic representations arise from learning associations between modality-specific representations, such as visual, praxic, function, verbal, which are situated in different cortical regions and communicate with each other via white-matter pathways within an interactive and distributed network. The base-connectivity hypothesis further argues that the communications between brain regions differ in their effectiveness so that brain regions with highly effective interconnections will cast mutual influence on each other and respond to similar stimuli in a similar way after learning the statistical structures in input stimuli. In another words, the resulting functional specialization of different parts in the same network can be greatly influenced by the base structure ([Plaut, 2002](#_ENREF_47); [Plaut & Behrmann, 2011](#_ENREF_48)). Furthermore, the base-connectivity hypothesis agrees that various confounding factors in the environmental structures may covary with semantic categories within and across sensory modalities, exerting another source for the functional specialization of cortical regions. For instance, the manmade objects are shown to have more function properties than animal concepts ([Cree & McRae, 2003](#_ENREF_17)) and their direct praxis requires more visual guidance ([Botvinick, Buxbaum, Bylsma, & Jax, 2009](#_ENREF_8)). As a result, learning the association of visual and praxic properties of this kind will strengthen the communications between corresponding cortical regions as some research has shown ([Mahon, Kumar, & Almeida, 2013](#_ENREF_33); [Mahon et al., 2007](#_ENREF_34)). Therefore, we argue that category-sensitive activation and category-selective impairment emerge from the joint efforts of the initial connectivity and learning of environmental structures in experience within a domain-general network.

In order to test the validity of the “base-connectivity hypothesis” in this paper, we will: (a) present evidence from the Activation Likelihood Estimate (ALE) meta-analysis of previous functional neuroimaging studies to delineate brain regions showing reliable category-sensitive activation across the board; (b) assess the connectivity within the cortical semantic network, especially, how modality-specific representations interact with each other and the cross-modal hub, namely, ventral ATL, by conducting a probabilistic tractography analysis of diffusion-weighted images (DWI); and (c) implement a neurocomputational model for semantic processing, which adopts the architecture revealed in the previous two analyses, and assess its ability to account for category-sensitive activation patterns and different patterns of semantic impairment in four patient groups, namely, SD patients with global semantic impairment, HSVE patients showing animal/living impairments, temporal tumor patients with deficits in manmade category, and pure alexic patients showing difficulty in recognizing living things.

**ALE Meta-analysis of category-sensitive activations**

The reliability of category-sensitive activation patterns remains in discussion ([Chouinard & Goodale, 2010](#_ENREF_14); [Gerlach, 2007](#_ENREF_22)), and the major challenge is to quantify the concordance of previous neuroimaging findings. In this section, we present a large-scale meta-analysis with 47 papers focusing on category activation patterns in human brain by using the Activation Likelihood Estimate (ALE) method ([Turkeltaub et al., 2012](#_ENREF_54)). A total of 110 foci for animal-related activation and 141foci for manmade-related activation were extracted from 56 independent experiments (32 fMRI and 24 PET) in those 47 papers (for details, see SI-method). Coordinates of foci were imported into the ALE meta-analysis package, gingerALE v2.3 ([Eickhoff et al., 2011](#_ENREF_19)) to calculate the main effects of animal-related and manmade-related activations contrasting with baseline conditions (see SI-Figure). The resultant main-effect ALE maps were then used to unveil cortical regions that yielded greater activation for both semantic categories (conjunction analysis) as well as the concordance of loci showing preferential activation patterns for animal concepts over the manmade ones and vice versa.

The common regions activated for both categories included only bilateral fusiform gyrus and the inferior frontal gyrus (see Figure 1 and Table S1). When the ALE map for main effect of animals was contrasted with that of manmade objects, several cortical regions in the posterior occipito-temporal conjunctions reliably showed greater activation for animal concepts (Figure 1 in red), including right posterior fusiform gyrus (pFG), superior temporal gyrus and middle temporal gyrus (STG/MTG) in the right hemisphere, and the left medial occipital gyrus (MOG). When the ALE map for manmade objects was compared to that of animal concepts, a somewhat different picture was uncovered: in addition to the medial aspect of pFG on both sides, the contrast revealed greater activation for manmade objects in the left middle temporal gyrus/inferior temporal gyrus (MTG/ITG) and inferior parietal lobule (IPL), especially the supramarginal gyrus. It seems that manmade objects recruit a more distributed neurocognitive network that incorporates regions in occipital, temporal, and parietal cortices that are less engaged by animal concepts.

The ALE meta-analysis provided empirical evidence that several cortical regions involves in category-sensitive representations of animals and manmade objects. Animal-related activations are generally related to ventral stream for visual processing: (a) lateral pFG was revealed in both main-effect and contrast ALE maps, although the category-sensitive activation seems to greatly overlap with manmade-related activation in the left hemisphere; (b) left MOG is likely to result from difference in visual properties (e.g., complexity) for early visual processing ([Chen & Rogers, 2014](#_ENREF_13)); and (c) activation around the superior temporal sulcus (STS) has been observed in the current meta-analysis on the right hemisphere (see Figure S1), and is largely driven by a few studies employing animation or video clips as stimuli for biological motions ([Grossman & Blake, 2002](#_ENREF_23); [Martin & Weisberg, 2003](#_ENREF_38)). Manmade objects, by contrast, yield a distributed cortical network including medial pFG which is sensitive to distinct visual features ([Mechelli et al., 2006](#_ENREF_43)), pMTG which may involve in representations of visual motion ([Martin & Weisberg, 2003](#_ENREF_38)) and action ([Bedny, Caramazza, Pascual-Leone, & Saxe, 2012](#_ENREF_4)), and IPL which shows enhanced activation to tools, function knowledge and manipulation of manmade objects ([Martin, 2007](#_ENREF_36)).

Although the meta-analysis helped us clarify where the brain regions showing category-sensitive activations are, we should interpret the ALE meta-analysis results with caution, especially for the results from the conjunction analysis. Note that coordinates from the 47 papers in this meta-analysis were those reported for category-sensitive activations. Therefore, it is very likely that some regions may play an important role in cortical semantic network across concept categories but cannot be revealed simply because they do not show category-sensitive activation at the first place. One of such region is the ventral aspect of the anterior temporal lobe (vATL) which is thought to be a “semantic hub” in the distributed semantic network ([Patterson et al., 2007](#_ENREF_46); [Rogers et al., 2004](#_ENREF_51)).

***Summary***. A widely distributed brain network was revealed from this meta-analysis for involving semantic processing of animal and manmade object concepts. Regions showing reliable preferential activation for animal concepts include lateral pFG on both hemispheres, right STG/STS, and regions for early-stage visual processing such as MOG. In comparison, manmade object concepts yield increased activation in medial pFG bilaterally, left MTG/ITG, and left IPL.

**Structural connectivity within cortical semantic network**

The ALE meta-analysis identified several cortical regions that may represent semantic knowledge about animal and manmade objects in multiple modalities, but how these brain regions interact with vATL, the hypothesized semantic hub, is poorly understood. In fact, only until recently, the relationship between abnormality in white-matter pathways central around vATL and deficits in semantic processing has been established ([Acosta-Cabronero et al., 2011](#_ENREF_2); [Han et al., 2013](#_ENREF_24); [Noppeney et al., 2007](#_ENREF_44)). Based on existing evidence, we propose three specific assumptions, focusing on how lateral parietal cortex interacts with ATL, to guide the current probabilistic tractography analysis on DWI data.

The intratemporal connections are relatively well understood in both non-human primates ([Felleman & Van Essen, 1991](#_ENREF_20)) and human subjects ([Binney, Parker, & Ralph, 2012](#_ENREF_7)). Specifically, evidence demonstrated intratemporal connectivity of medial and lateral rostral temporal lobe with pFG (i.e., the ventral visual pathway) as well as connectivity between lateral rostral temporal lobe and superior temporal gyrus (STG) and Heschl’s gyrus (HG), also known as the primary auditory cortex ([Binney et al., 2012](#_ENREF_7)). Therefore, the interaction of the semantic hub (vATL) with visual (e.g., fusiform gyrus) and auditory (STG, HG) representations is well documented.

In comparison, direct connection between the vATL and lateral parietal cortex (LP) is rarely observed, suggesting that the praxic and function representations of object knowledge only indirectly interact with the semantic hub. One proposed possibility is that LP interacts with vATL via medial pFG based on established functional connectivity ([Mahon et al., 2013](#_ENREF_33); [Mahon et al., 2007](#_ENREF_34)), which seems to have anatomical basis in other primates ([Felleman & Van Essen, 1991](#_ENREF_20); [Zhong & Rockland, 2003](#_ENREF_58)). Another possibility is information from IPL integrates into vATL via pMTG as implicitly suggested in the brain of the macaque monkey ([Seltzer & Pandya, 1994](#_ENREF_52)), and observed in human subjects ([Binney et al., 2012](#_ENREF_7)): Caudal MTG has high probability of connection with supramarginal gyrus (SMG) and angular gyrus (AG) in IPL. Both possibilities seem compatible with the ALE meta-analysis in that preferential activation for manmade objects has been reported for all three regions, namely, medial pFG, MTG, and LP (i.e., IPL). The third possibility comes from structural imaging ([Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004](#_ENREF_56)) and human brain dissection studies ([Duffau, Herbet, & Moritz-Gasser, 2013](#_ENREF_18); [Martino, Brogna, Robles, Vergani, & Duffau, 2010](#_ENREF_40)), revealing that the dorsal branch of inferior frontal-occipital fasciculus (IFOF) opens like a fan and streams into various regions in parietal lobe, particularly the superior parietal lobe (SPL) rather than the inferior aspect, and the starting site of dorsal branch seems a little bit more anterior to the medial pFG site observed in our ALE analysis. We therefore also explored the possibility that the medial aspect of pFG may interact with the SPL.

The present probabilistic tractography analysis is based on diffusion-weighted images (DWI) from 24 right-handed healthy subjects (11 female; mean age = 25.9) at University of Manchester, England ([Cloutman, Binney, Morris, Parker, & Lambon Ralph, 2013](#_ENREF_16)) in a 3T Philips Achieva scanner (Philips Medical Systems, Best, Netherlands), using an 8 element SENSE head coil (details of scanning procedures in SI-method). The seed region of interests (ROIs) are chosen from: (a) ALE meta-analysis in previous section, including lateral pFG, medial pFG, MOG, pMTG and IPL (IPL\_1) in the left hemisphere; (b) previous literature, including one ROI in vATL from an fMRI study ([Visser, Jefferies, & Lambon Ralph, 2010](#_ENREF_55)) and a second ROI for IPL seed (IPL\_2) from a transcranial stimulation study ([Pobric, Jefferies, & Lambon Ralph, 2010](#_ENREF_49)) given the uncertainty of how LP is incorporated in the cortical semantic network. ROIs are defined as a sphere with a diameter of 6 mm in MNI brain space (Montreal Neurological Institute) and then converted into native space of each individual subject. For each voxel within a seed ROI sphere, 15,000 streamlines were initiated using unconstrained probabilistic tractography with a dedicated software package using the PICo (Probabilistic Index of Connectivity) method ([Parker & Alexander, 2005](#_ENREF_45)). On the unnormalized tracking data from each seed region of each individual, other ROI masks were overlaid and a maximum connectivity value (ranging from 0 to 15,000) was obtained for the seed region and each of other ROIs, resulting in a matrix of streamline-based connectivity. A two-level threshold (individual level: 1%, 2.5%, and 5% for high probability; and group level: exceed high probability criterion in at least 12 subjects, i.e., 50% of the subject sample) was applied to determine high likelihood of connection based on heuristic distributions established by previous study ([Cloutman, Binney, Drakesmith, Parker, & Lambon Ralph, 2012](#_ENREF_15)) using the same method and dataset (**Put in SI or Figures??**) (for more details, see SI-method).

The connectivity matrix is presented in Table S2-3 and the group-averaged probabilistic tractography is shown in Figure 2.

***Intratemporal connections between vATL, pFG, MTG, and MOG****.* Figure 2A shows the group-averaged tractography streamlines coming out from lateral (purple) and medial pFG (cyan). As expected, lateral and medial pFG are highly interconnected with each other, and more importantly, both lateral and medial pFG project into the vATL seed region with high probability (> 5% in more than two thirds of the participants). This interconnection between ATL and pFG seed regions is bidirectional, in that the streamlines generated from ATL also projected into both pFG seeds as well. Although the seed for MTG in this analysis is more posterior than that used in Binney et al. ([2012](#_ENREF_7)), we still observed connectivity between vATL and MTG with high probability (from vATL to MTG, >2.5% in more than half participants in Table S2); likewise the streamlines from MTG proceeded into the anterior temporal region and terminated in the neighborhood of the vATL seed (yellow-colored in Figure 2B). The connection between MTG and pFG was also observed: the connection of MTG with lateral pFG was highly probably whereas the one with medial pFG was only observed consistently across participants with the most relaxed criterion (> 1% in more than half participants). Given that the medial and lateral pFG are highly interconnected, we assume an intensive communication between pFG and MTG, regardless of lateralization. The MOG seems to have restricted connections within occipital cortex (orange in Figure 2A) and only shows probable connection with lateral pFG bidirectionally at a relaxed threshold.

***Indirect connection between vATL and IPL via MTG and pFG.*** The above section reviewed direct connections with vATL, none of which involved the IPL seeds. Thus the results are consistent with the view that there is no direct connection between vATL and lateral parietal cortex. We next tested the first assumption about an indirect route from IPL to vATL via MTG. The direct connection between vATL and MTG was shown in Figure 2B (in yellow), and the same figure also depicts the connection between IPL seeds and MTG (in green). From Figure 2D, we can also see that the mutual communication between MTG and IPL, especially the IPL\_2 seed, is highly probable. Therefore, the indirect interaction between vATL and lateral parietal cortex can be substantiated by this white matter pathway via MTG. In contrast, the other possibility that indirect interactions between vATL and IPL may be mediated via pFG was not confirmed in the current analysis. From Figure 2B, we can clearly see that streamlines from medial pFG and IPL seeds did not project into each other with high probability even at the relaxed threshold. Therefore, the puzzle about how LP interacts with medial pFG—as suggested by the functional connectivity in neuroimaging studies—awaits further investigation.

***Interconnection between SPL and medial pFG.***Here, we explored the third possibility driven by structural evidence that the medial aspect of pFG may interact with the superior aspect of lateral parietal cortex instead of the inferior aspect. Accordingly, three seed regions informed by this structural imaging evidence were added (see Table S3 and SI-method): two ROIs in SPL (SPL\_1 and SPL\_2) and a more anterior ROI for medial pFG (medial pFG\_2). Figure 2C presents the group-averaged tractography from both medial pFG and SPL seeds. Streamlines from SPL\_1 project into the medial aspect of ventral temporal cortex and get quite close to the medial pFG\_2 seed region. The streamlines from medial pFG\_2, in turn, proceed into medial pFG and parietal lobe; however the dorsal branch terminates slightly medial than the SPL\_1 seed. The analysis thus reveals a circuit comprising SPL and medial pFG, all of which have been associated with category-specific activation for manmade objects in the literature. Although the termination points of streams from parietal and anterior medial pFG regions did not lie precisely within the complementary seed regions, this may be attributable to the fan-shaped dorsal stream of IFOF, with the current analysis picking up two minor branches of the same stream.

***Summary.*** The probabilistic tractography results accord well with the proposals that (a) pFG and MTG have direct connections with ATL, whereas lateral parietal cortex (especially, IPL) is not directly connected to ATL, and (b) one seed of lateral parietal cortex, IPL, may interact with ATL indirectly via MTG. The analysis also revealed additional circuitry involving medial pFG and another seed in superior lateral parietal cortex, SPL—suggesting one way that lateral parietal cortex may communicate with medial pFG and indirectly with ATL.

**Simulations of category-sensitive functional activations**

Here, we propose a neurocomputational model of semantic cognition with its architecture constrained by the knowledge learned from the results of both ALE meta-analysis and DWI probabilistic tractography (summarized in Figure 3A). This neurocomputational model will further allow us to test the “base connectivity hypothesis” by assessing its ability to account for category-sensitive activation patterns observed in healthy individuals without neuropsychological deficits as well as category-specific impairments in the patient groups with different etiologies.

Figure 3B depicts the final architecture we propose to account for semantic processing and category-sensitive activation patterns for animals and manmade objects in neuroimaging studies. The pFG ROIs (both lateral and medial) were entered into the probabilistic tractography analysis and shown to be connected with vATL and MTG, consistent with its role as part of the ventral visual pathway for object recognition. The vATL semantic hub also directly interacts with STG, which receives direct auditory/linguistic inputs as part of the perisylvian language system ([Catani, Jones, & ffytche, 2005](#_ENREF_11)). No direct connection between LP and ATL is assumed; instead, MTG is added and connected with vATL, pFG, and IPL so that the inferior aspect of LP interacts with vATL via MTG; and pFG has graded connectivity with SPL in order to reflect the circuitry of medial pFG and SPL revealed by our tractography analysis. The current architecture about how LP may be incorporated in cortical semantic network echoes the proposals of Buxbaum and colleagues ([Binkofski & Buxbaum, 2013](#_ENREF_6)) who distinguish two dorsal routes for visually-guided action. The ventral-dorsal pathway passes visual information to IPL (especially, supramarginal gyrus) which appears to represent object function, aligning with the route from pFG to IPL via MTG in our probabilistic tractography analysis. The dorso-dorsal pathway communicates visual information to the SPL and then extends into postcentral gyrus and primary motor cortex. The circuitry of medial pFG and SPL seemingly corresponds to this pathway, which is associated with direct and online motor control for executing actions. Therefore, in the current model, we specify two LP components, namely the IPL which processes information about object functions and the SPL which involves in presenting direct visually-guided praxic information.

The current model simulation aims to capture the following benchmark phenomena of category-sensitive activation patterns which have greatly impact on theoretical interpretations about the organization of cortical semantic network: (a) category-specific activations in a wide range of cortical regions including lateral pFG for animal concepts, and medial pFG, pMTG, IPL and SPL for manmade objects as revealed in out meta-analysis and previous literature ([Chouinard & Goodale, 2010](#_ENREF_14); [Mahon et al., 2010](#_ENREF_35)); (b) similar cortical responses to visual and verbal stimuli for animal and manmade objects ([Mahon et al., 2009](#_ENREF_30)); and (c) similar and different activation patterns between sighted individuals and congenitally blind people, specifically, the absence of animal-related activation in lateral pFG and presence of manmade-related activations in medial pFG, pMTG, IPL and SPL in the blind ([Bedny et al., 2012](#_ENREF_4); [Mahon et al., 2009](#_ENREF_30); [Mahon et al., 2010](#_ENREF_35)).

All models were trained to associate verbal (name and descriptions), visual, function and praxic representations for the same set of 48 items, including 24 model “animals” and 24 model “manmade objects.” A unique pattern of activation over visual and verbal units were firstly created for each item, with animals sharing more visual properties overall than manmade objects ([McRae, de Sa, & Seidenberg, 1997](#_ENREF_42)). Praxic and function representations were generated for each manmade objects by copying the item’s visual properties and flipping the state of each unit with a small probability (p = 0.2). To simulate the difference between the sighted and congenitally blind, we trained fully-sighted model variants with all varieties of input and output (namely, visual, verbal, function, and praxic), while congenitally-blind model variants were trained on all associations but visual, i.e., no inputs or targets were applied to visual units in these models. To capture the finding that medial pFG has connections with SPL with high probability compared to the lateral pFG, units in the visual hidden layer varied along an anatomical lateral/medial axis, and the learning rate (and hence connectivity) in the visuo-praxic path diminished for more lateral units (see SI-method for more details). All units had a fixed negative bias to promote low activations without external inputs, and all models were trained to produce the correct outputs with high accuracy. The functional activation patterns were measured in each corresponding hidden layers by calculating the unit activations in two tasks, namely visual viewing task when external inputs were provided only from visual modality (for sighted model variants) and name comprehension task when name of each item was probed from the verbal modality (for both sighted and blind model variants). Fifteen models of each kind were trained, differing only in their initial weights, to simulate fifteen different participants in an imaging study.

Figure 4A depicts the averaged unit activation patterns in pFG, MTG, IPL, and SPL hidden layers when the sighted models were tested with the visual viewing task. The pattern in pFG replicated what we observed in the ALE meta-analysis: lateral pFG yielded increased activation for animal exemplars whereas the medial units in pFG hidden layers showed preferential activation for manmade object exemplars. This functional specialization results from the effective connectivity between pFG and SPL hidden layers due to the pressure for learning the cross-mapping between visual and praxic representations. Meanwhile, the other three hidden layers, pMTG, IPL, and SPL showed stronger activation when the visual input patterns were of manmade objects. It is not surprising that the IPL and SPL hidden units showed stronger activations for manmade objects since these interacted directly with visible units encoding functional and praxic representations that were only active for manmade items. The pMTG hidden layer, however, could mediate the propagation of visual information from pFG to vATL in a similar manner for both animal and manmade object concepts. The crucial pressure producing the category-specific pattern came from two sources. First, learning cross-mappings among function representations and verbal features requires the indirect route from STG to IPL via both ATL and pMTG. Second, the mappings between function and visual representations for manmade objects from pFG to IPL can potentially be learned more efficiently through MTG. Although visual-verbal interactions for animal concepts could potentially be mediated by the MTG hidden layers, the pathway via the ATL is more efficient given the direct connection between pFG and ATL. For these reasons, MTG hidden layers, though not natively constrained to respond differently to the two domains, gradually tunes to be responsive to manmade object concepts. A similar pattern across these target regions was observed when sighted models were tested in the name comprehension task as well (see Figure 4B). Figure 4C showed the result from the blind variant of this neurocomputaional model when tested with the name comprehension task. The overall activation patterns look rather similar to the sighted variant with the only exception that the category-specific activation for animal concepts was largely reduced in the lateral pFG, which showed little differential activation across two concept domains.

***Summary.*** From the perspective of the “base connectivity hypothesis”, we proposed an anatomically constrained neurocognitive network for semantic processing that provides a relatively comprehensive account of category-specific activation patterns in neuroimaging studies. Based on the findings from both ALE meta-analysis and DWI probabilistic tractography, we established a neurocomputational model whose architecture reflects the white matter pathways between core brain regions in the cortical semantic network. Results showed that category-sensitive activation patterns in a broader range of brain regions can be successfully simulated in this model. More importantly, not only did this model capture the presence of category-specific activation for sighted population with both visual and verbal stimuli, but also accurately reproduced the presence and absence of category-sensitive activation in the congenitally blind individuals.

**Simulations of category-specific impairments**

Our neurocomputational model is the pioneer attempt to account for functional activation patterns in human brain, while previous neural network models have been quite successful in account for various behavioral patterns of semantic deficits. Therefore, an outstanding question for us is to investigate how well our neurocomputational model based on the “base connectivity hypothesis” can also account for a wide spectrum of semantic deficit patterns observed in neuropsychological research.

The four patient groups examined here, namely, semantic dementia (SD), Herpes Simplex Virus Encephalitis (HSVE), lateral posterior temporal Tumor (LP\_Tumor) and pure alexia (PA), show reliable patterns of semantic deficits and symptom-lesion studies have established the relationship between their deficits and abnormality in different white-matter pathways. The SD patients have focal atrophy in anterior temporal pole which affect almost all efferent and afferent white-matter pathways from and to the vATL ([Acosta-Cabronero et al., 2011](#_ENREF_2); [Noppeney et al., 2007](#_ENREF_44)), and they show cross-board impairment for all semantic categories in semantic tasks like object naming. On the contrary, the HSVE patients who also have a pathology affecting the temporal lobe, although more diffusive, general show much lower accuracy in naming animal items compared to naming manmade objects. Study has demonstrated that the HSVE case had greater decrease in white matter volume on the lateral side of left temporal lobe ([Noppeney et al., 2007](#_ENREF_44)). This white matter loss is of particular interest to our neurocomputational model for its clear suggestion that the white matter pathway in the lateral aspect of ventral visual stream may account for the category-specific impairment of animal concepts in HSVE patients. To our knowledge, the most relevant and compelling evidence for the lesion-symptom correspondence of manmade-object deficit is provided by Tim Shallice and his colleagues ([Campanella et al., 2010](#_ENREF_9)), showing that patients who had undergone surgical removal of temporal tumors demonstrated a significant category-specific impairment for the nonliving category, especially for those with tumor location in the left posterior temporal lobe (the deficit is mild though for the full range of difference score was about 2% ~ 21% for living vs. nonliving contrast in object naming). More importantly, voxels in posterior tempo-parietal white matters, specifically, white-matter connections between pMTG and IPL, were found to be correlated with deficit of nonliving things as well. This finding strikingly with our ALE meta-analysis and probabilistic tractography analysis: the posterior MTG and IPL are interconnected with each other and show category-specific activations for manmade objects in neuroimaging studies. Thus, a reasonable working hypothesis that can be tested in the model is that focal lesion in this posterior tempo-parietal sub-network produce category-specific impairment to nonliving category. The pure alexic patients general have lesion in early visual cortex, and a possible cause for their animal-related deficit is the failure to integrate low-level features into high-level object percepts, a process more difficult for animal objects due to their complex and overlapping structures in visual information (??Refs). One distinct property of animal-related deficit in pure alexia is that, in the object naming task, they show comparable accuracy for animal and manmade objects, but the naming latency for animal items was slower. Therefore, for the current model simulation, the target behavioral patterns in object naming task in four patient groups are: (a) a global semantic deficit in naming accuracy for SD patients; (b) a much reduced naming accuracy for animal items in HSVE patients; (c) a mild deficit in naming accuracy for manmade objects compared to animals in TT patients; and (d) a slower naming latency, but a comparable naming accuracy, for animals in PA patients.

The same neurocomputational model architecture used to account for the category-sensitive activation patterns was used for this simulation, and a similar training procedure for sighted variants was used (for details see SI-method). After the model was trained to successfully learn the cross-mappings between visual, verbal, function and praxic representations of both animal and manmade objects, an object naming task was used to test the model performance when lesions were applied to different loci in the model connections. In this naming task, external visual inputs were provided to the model and the correct/wrong performance was scored based on the activation of corresponding item names (higher than 0.5 was scored as correct; otherwise as wrong). To simulate the SD case, afferent and efferent connections of ATL were randomly pruned out, affecting all direct interactions with pFG (both lateral and medial), MTG, and STG (at locations A, B, C in red in Figure 3B). To simulate the HSVE case, connections between lateral pFG units and ATL units (lateral part of location C in red in Figure 3B) were randomly pruned out to reflect the finding that lateral aspect of the white matter pathway in ventral temporal lobe was severely affected in HSVE patients. The simulation of LP\_Tumor patients was conducted by pruning out connections coming in and going out from MTG and IPL layers (at locations B and D in red in Figure 3B) in order to simulate the lesion site in posterior tempo-parietal regions, especially the connections between MTG and IPL. In all three types of lesion, the connection weights were randomly deleted from 10% to 100% with an increment of 10%. Because of the distinct property of animal-related deficit in PA patients, we used a slightly different lesion procedure for the model simulation: The afferent connections into pFG hidden layer from visual inputs were random pruned out (at location E in red in Figure 3B), but with an increment of 2.5% from 2.5% to 25% in order to simulate decreasing low-level visual signal while to preserve sufficient signal from visual inputs. The naming latency was calculated by recording the number of time ticks when the model settled on the right name units (for more details, see SI-methods).

Figure 4D-G showed the naming accuracy for animal and manmade objects in simulation of SD, HSVE and LP\_Tumor cases as a function of lesion severity, and Figure 3H showed both naming latency in simulation of PA cases. In addition, averaged accuracy collapsing across levels of severity for all simulated data was plot against the mean accuracy of corresponding patient groups in empirical data (see SI-method). In Figure 4D, we can observe a fast decline of naming accuracy for both animal and manmade object categories when lesion was applied to all efferent and afferent connections from and to vATL layer although the overall accuracy for manmade objects was slightly higher than animals (for animal vs. manmade difference, Mdiff. = -0.057, range = -0.097 ~ -0.041). This pattern is in accordance with the empirical data on SD patients as demonstrated in the small bar graph. By contrast, a sizeable category-specific effect for animal concepts was observed when the lesion was applied to the connections between lateral pFG units and ATL (Figure 4E), Mdiff. = -0.413, range = -0.558~-0.207). This result resembles findings in previous studies as well. For the lesions in the MTG/IPL connections (Figure 4F), a model analog of damage in the LP\_Tumor cases, a mild category-specific impairment to manmade object concepts was observed: for the animal vs. manmade difference, the averaged mean was 0.072 (range = 0.03~0.196), which is largely consistent with the reported data from Campenella et al. By and large, a double dissociation pattern of category-specific impairment was observed in the simulations of HSVE and LP\_Tumor cases in this model, as well as a profound category-general impairment when weights of ATL were affected proportionally across all modalities. Figure 4G showed naming latency in the model when lesion was applied to afferent connections to pFG layer from visual inputs: the naming latency for animal items were noticeable slower at the very mild level of lesion compared to naming manmade objects, and the discrepancy increased enormously as the lesion severity increased (Mdiff. = 2.750, range = 0.620~ 4.648). This is largely coherent with the empirical data showing that the naming deficit for animal concepts in PA patients can be observed on latency data but not on accuracy, especially when the lesion severity was mild (Refs). Figure 4H&I depicted the lesion-symptom correlation in model and patient groups respectively. Basically, great similarity between and patient data was observed that lesion severity is (a) not correlated with naming accuracy difference between animal and manmade object items in SD; (b) associated with increase in difficulty in naming animals in HSVE; and (c) associated with increasing impairment in naming manmade objects in LP\_Tumor patients. (Maybe in SI?)

***Summary.*** From the results in this section, we can see how the same neurocomputational model that can account for category-sensitive activation patterns in human brain also demonstrated great capacity of explaining a whole spectrum of reliable semantic deficit patterns that have been documented in the literature in all four different patient groups. This evidence further validates the “base connectivity hypothesis” which assumes that the white-matter connectivity within cortical semantic network constrains how specialization of knowledge representations for different categories is distributed across the whole network.

**General discussion**

By integrating techniques of neuroimaging (both functional and structural) and computational models, our work indicates that architectural constraints have fundamental implications about the neural organization and function of cortical semantic network: Interconnected brain regions in the widely-distributed network tend to show similar profiles of functional activation to different semantic categories, and selective disruptions of corresponding architecture produce the whole spectrum of semantic impairment patterns that are reliably observed in brain-damaged patients. Built on existing domain-general views ([Patterson et al., 2007](#_ENREF_46)), our “base-connectivity hypothesis” demonstrated how category-specific activation and impairment can emerge from a single interactive neurocognitive network as a result of both learning cross-mappings between modality-specific representations in the environment and the architectural constraints of network in the current data. Despite of theoretical advance from domain-specific views, our work provides a single model to account for converging evidence from neuroimaging, model simulation and patient studies about neural representations of semantic knowledge as well as a unified framework for incorporating neural imaging and computational techniques, which can be potentially extended beyond cortical semantic network (see Figure 5).

Our “base-connectivity hypothesis” relates but still contrasts to recent claim from domain-specific views about how certain brain connectivity may mediate the functional specialization in visual ventral stream ([Mahon & Caramazza, 2011](#_ENREF_32)) in significant ways. First, there is no doubt that functional specialization in neural network is largely influenced by the connectivity, but we believe that the constraints of network connectivity are not designed for certain semantic domain; instead, the connectivity structure enables more effective learning of covariance structure across different sensory/motor modalities (e.g., visual, haptic). Along with the systematic difference across semantic categories in the cross-modal covariance structure, the base connectivity shapes the functional specialization in cortical semantic network. Again, it is the joint force of brain network structure and learning experience in environment. Therefore, the privileged connectivity concerns more about the manner in which we interact with different objects rather than fixed semantic domains. Second, regardless of whether the domain-specificity refers to the property of brain modules or connectivity, the influence of experience and learning always seems to be downplayed by the domain-specific views because those modules or connectivity are generally assumed to be innately disposed ([Caramazza & Shelton, 1998](#_ENREF_10); [Mahon et al., 2009](#_ENREF_30); [Mahon & Caramazza, 2011](#_ENREF_32)). Not only do we argue that learning experience contributes to the functional specialization in cortical semantic network, but also we acknowledge the role of experience in shaping the architecture. As shown in Figure 4, our model accounts for the functional specialization in visual ventral stream can be modulated by visual experience (i.e., lack of animal-related advantage in lateral pFG) which is unexplained by domain-specific views. Furthermore, we believe that learning and experience can shape the architecture of neurocognitive network ([Abrams et al., 2013](#_ENREF_1); [Tang et al., 2010](#_ENREF_53)) although our data do not directly address this issue. Third, our data speaks more in-detail about how the action and praxic information from parietal cortex integrates into ventral temporal stream. Current domain-specific views only concern about the connectivity between IPL and medial pFG for representing tool concepts, but our view further allows us to understand a possible dual sub-networks involving IPL and SPL which is more consistent with other theory about action representations ([Binkofski & Buxbaum, 2013](#_ENREF_6)).

**Conclusion**

We provide converging evidence here to demonstrate how category-specificity can emerge from a distributed neurocognitive network of semantics in order to reveal how architecture of cortical semantic network may place constraints on the functional specialization. Brain regions like medial pFG, pMTG, IPL and SPL may be preferred structures to represent manmade objects due to the interconnections and highly-covarying structures across different modalities. Disruptions to specialized subnetwork connectivity leads to different patterns of category-specific impairment.

References and Notes:

Abrams, D. A., Lynch, C. J., Cheng, K. M., Phillips, J., Supekar, K., Ryali, S., . . . Menon, V. (2013). Underconnectivity between voice-selective cortex and reward circuitry in children with autism. *Proceedings of the National Academy of Sciences, 110*(29), 12060-12065.

Acosta-Cabronero, J., Patterson, K., Fryer, T. D., Hodges, J. R., Pengas, G., Williams, G. B., & Nestor, P. J. (2011). Atrophy, hypometabolism and white matter abnormalities in semantic dementia tell a coherent story. *Brain, 134*(7), 2025-2035.

Adlam, A. L. R., Patterson, K., Rogers, T. T., Nestor, P. J., Salmond, C. H., Acosta-Cabronero, J., & Hodges, J. R. (2006). Semantic dementia and fluent primary progressive aphasia: two sides of the same coin? *Brain, 129*(11), 3066-3080.

Bedny, M., Caramazza, A., Pascual-Leone, A., & Saxe, R. (2012). Typical Neural Representations of Action Verbs Develop without Vision. *Cerebral Cortex, 22*(2), 286-293. doi: 10.1093/cercor/bhr081

Behrmann, M., & Plaut, D. C. (2012). Bilateral Hemispheric Processing of Words and Faces: Evidence from Word Impairments in Prosopagnosia and Face Impairments in Pure Alexia. *Cerebral Cortex*. doi: 10.1093/cercor/bhs390

Binkofski, F., & Buxbaum, L. J. (2013). Two action systems in the human brain. *Brain and Language, 127*(2), 222-229.

Binney, R. J., Parker, G. J., & Ralph, M. A. L. (2012). Convergent connectivity and graded specialization in the rostral human temporal lobe as revealed by diffusion-weighted imaging probabilistic tractography. *Journal of Cognitive Neuroscience, 24*(10), 1998-2014.

Botvinick, M. M., Buxbaum, L. J., Bylsma, L. M., & Jax, S. A. (2009). Toward an integrated account of object and action selection: A computational analysis and empirical findings from reaching-to-grasp and tool-use. *Neuropsychologia, 47*(3), 671-683.

Campanella, F., D’Agostini, S., Skrap, M., & Shallice, T. (2010). Naming manipulable objects: Anatomy of a category specific effect in left temporal tumours. *Neuropsychologia, 48*(6), 1583-1597.

Caramazza, A., & Shelton, J. R. (1998). Domain-specific knowledge systems in the brain: The animate-inanimate distinction. *Journal of Cognitive Neuroscience, 10*(1), 1-34.

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology, 57*(1), 8-16. doi: 10.1002/ana.20319

Chao, L. L., & Martin, A. (2000). Representation of manipulable man-made objects in the dorsal stream. *Neuroimage, 12*(4), 478-484.

Chen, L., & Rogers, T. T. (2014). Revisiting domain‐general accounts of category specificity in mind and brain. *Wiley Interdisciplinary Reviews: Cognitive Science, 5*(3), 327-344.

Chouinard, P. A., & Goodale, M. A. (2010). Category-specific neural processing for naming pictures of animals and naming pictures of tools: An ALE meta-analysis. *Neuropsychologia, 48*(2), 409.

Cloutman, L. L., Binney, R. J., Drakesmith, M., Parker, G. J., & Lambon Ralph, M. A. (2012). The variation of function across the human insula mirrors its patterns of structural connectivity: Evidence from in vivo probabilistic tractography. *Neuroimage, 59*(4), 3514-3521.

Cloutman, L. L., Binney, R. J., Morris, D. M., Parker, G. J., & Lambon Ralph, M. A. (2013). Using< i> in vivo</i> probabilistic tractography to reveal two segregated dorsal ‘language-cognitive’pathways in the human brain. *Brain and Language*.

Cree, G. S., & McRae, K. (2003). Analyzing the factors underlying the structure and computation of the meaning of chipmunk, cherry, chisel, cheese, and cello (and many other such concrete nouns). *Journal of Experimental Psychology: General, 132*(2), 163-201.

Duffau, H., Herbet, G., & Moritz-Gasser, S. (2013). Toward a pluri-component, multimodal, and dynamic organization of the ventral semantic stream in humans: lessons from stimulation mapping in awake patients. *Frontiers in systems neuroscience, 7*.

Eickhoff, S. B., Bzdok, D., Laird, A. R., Roski, C., Caspers, S., Zilles, K., & Fox, P. T. (2011). Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *Neuroimage, 57*(3), 938-949.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed Hierarchical Processing in the Primate Cerebral Cortex. *Cerebral Cortex, 1*(1), 1-47. doi: 10.1093/cercor/1.1.1

Gauthier, I., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. [10.1038/72140]. *Nat Neurosci, 3*(2), 191-197. doi: <http://www.nature.com/neuro/journal/v3/n2/suppinfo/nn0200_191_S1.html>

Gerlach, C. (2007). A review of functional imaging studies on category specificity. *Journal of Cognitive Neuroscience, 19*(2), 296-314.

Grossman, E. D., & Blake, R. (2002). Brain areas active during visual perception of biological motion. *Neuron, 35*(6), 1167-1175.

Han, Z., Ma, Y., Gong, G., He, Y., Caramazza, A., & Bi, Y. (2013). White matter structural connectivity underlying semantic processing: Evidence from brain damaged patients. *Brain*, awt205.

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science, 293*(5539), 2425.

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia progressive fluent aphasia with temporal lobe atrophy. *Brain, 115*(6), 1783-1806.

Kanwisher, N. (2010). Functional specificity in the human brain: A window into the functional architecture of the mind. *Proceedings of the National Academy of Sciences of the United States of America, 107*(25), 11163-11170. doi: 10.1073/pnas.1005062107

Laiacona, M., Capitani, E., & Caramazza, A. (2003). Category-specific Semantic Deficits do not Reflect the Sensory/Functional Organization of the Brain: A Test of the “Sensory Quality” Hypothesis. *Neurocase, 9*(3), 221-231. doi: 10.1076/neur.9.3.221.15562

Lambon Ralph, M. A., Lowe, C., & Rogers, T. T. (2007). Neural basis of category-specific semantic deficits for living things: Evidence from semantic dementia, HSVE and a neural network model. *Brain, 130*, 1127-1137. doi: 10.1093/brain/awm025

Mahon, B. Z., Anzellotti, S., Schwarzbach, J., Zampini, M., & Caramazza, A. (2009). Category-Specific Organization in the Human Brain Does Not Require Visual Experience. *Neuron, 63*(3), 397-405. doi: 10.1016/j.neuron.2009.07.012

Mahon, B. Z., & Caramazza, A. (2009). Concepts and categories: A cognitive neuropsychological perspective. *Annual Review of Psychology, 60*(1), 27-51. doi: 10.1146/annurev.psych.60.110707.163532

Mahon, B. Z., & Caramazza, A. (2011). What drives the organization of object knowledge in the brain? *Trends in Cognitive Sciences, 15*(3), 97-103. doi: <http://dx.doi.org/10.1016/j.tics.2011.01.004>

Mahon, B. Z., Kumar, N., & Almeida, J. (2013). Spatial Frequency Tuning Reveals Interactions between the Dorsal and Ventral Visual Systems. *Journal of Cognitive Neuroscience*, 1-10. doi: 10.1162/jocn\_a\_00370

Mahon, B. Z., Milleville, S. C., Negri, G. A. L., Rumiati, R. I., Caramazza, A., & Martin, A. (2007). Action-related properties shape object representations in the ventral stream. *Neuron, 55*(3), 507-520.

Mahon, B. Z., Schwarzbach, J., & Caramazza, A. (2010). The Representation of Tools in Left Parietal Cortex Is Independent of Visual Experience. *Psychological Science, 21*(6), 764-771. doi: 10.1177/0956797610370754

Martin, A. (2007). The Representation of Object Concepts in the Brain. *Annual Review of Psychology, 58*(1), 25-45. doi: 10.1146/annurev.psych.57.102904.190143

Martin, A., Haxby, J. V., Lalonde, F. M., Wiggs, C. L., & Ungerleider, L. G. (1995). Discrete Cortical Regions Associated with Knowledge of Color and Knowledge of Action. *Science, 270*(5233), 102-105. doi: 10.2307/2888224

Martin, A., & Weisberg, J. (2003). Neural foundations for understanding social and mechanical concepts. *Cognitive Neuropsychology, 20*(3-6), 575-587.

Martin, A., Wiggs, C. L., Ungerleider, L. G., & Haxby, J. V. (1996). Neural correlates of category-specific knowledge. [10.1038/379649a0]. *Nature, 379*(6566), 649-652.

Martino, J., Brogna, C., Robles, S. G., Vergani, F., & Duffau, H. (2010). Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex, 46*(5), 691-699.

McClelland, J. L., & Rogers, T. T. (2003). The parallel distributed processing approach to semantic cognition. [10.1038/nrn1076]. *Nat Rev Neurosci, 4*(4), 310-322.

McRae, K., de Sa, V. R., & Seidenberg, M. S. (1997). On the nature and scope of featural representations of word meaning. *Journal of Experimental Psychology: General, 126*(2), 99-130. doi: 10.1037/0096-3445.126.2.99

Mechelli, A., Sartori, G., Orlandi, P., & Price, C. J. (2006). Semantic relevance explains category effects in medial fusiform gyri. *Neuroimage, 30*(3), 992-1002. doi: 10.1016/j.neuroimage.2005.10.017

Noppeney, U., Patterson, K., Tyler, L. K., Moss, H., Stamatakis, E. A., Bright, P., . . . Price, C. J. (2007). Temporal lobe lesions and semantic impairment: a comparison of herpes simplex virus encephalitis and semantic dementia. *Brain, 130*(4), 1138-1147.

Parker, G. J., & Alexander, D. C. (2005). Probabilistic anatomical connectivity derived from the microscopic persistent angular structure of cerebral tissue. *Philosophical Transactions of the Royal Society B: Biological Sciences, 360*(1457), 893-902.

Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat Rev Neurosci, 8*(12), 976-987.

Plaut, D. C. (2002). Graded modality-specific specialisation in semantics: A computational account of optic aphasia. *Cognitive Neuropsychology, 19*(7), 603-639.

Plaut, D. C., & Behrmann, M. (2011). Complementary neural representations for faces and words: A computational exploration. *Cognitive Neuropsychology, 28*(3-4), 251-275.

Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2010). Category-Specific versus Category-General Semantic Impairment Induced by Transcranial Magnetic Stimulation. *Current Biology, 20*(10), 964-968.

Rogers, T. T., Hocking, J., Mechelli, A., Patterson, K., & Price, C. (2005). Fusiform Activation to Animals is Driven by the Process, Not the Stimulus. *Journal of Cognitive Neuroscience, 17*(3), 434-445. doi: doi:10.1162/0898929053279531

Rogers, T. T., Lambon Ralph, M. A., Garrard, P., Bozeat, S., McClelland, J. L., Hodges, J. R., & Patterson, K. (2004). Structure and deterioration of semantic memory: A neuropsychological and computational investigation. *Psychological Review, 111*(1), 205-235. doi: 10.1037/0033-295x.111.1.205

Seltzer, B., & Pandya, D. N. (1994). Parietal, temporal, and occipital projections to cortex of the superior temporal sulcus in the rhesus monkey: A retrograde tracer study. *The Journal of Comparative Neurology, 343*(3), 445-463. doi: 10.1002/cne.903430308

Tang, Y.-Y., Lu, Q., Geng, X., Stein, E. A., Yang, Y., & Posner, M. I. (2010). Short-term meditation induces white matter changes in the anterior cingulate. *Proceedings of the National Academy of Sciences, 107*(35), 15649-15652. doi: 10.1073/pnas.1011043107

Turkeltaub, P. E., Eickhoff, S. B., Laird, A. R., Fox, M., Wiener, M., & Fox, P. (2012). Minimizing within‐experiment and within‐group effects in activation likelihood estimation meta‐analyses. *Human Brain Mapping, 33*(1), 1-13.

Visser, M., Jefferies, E., & Lambon Ralph, M. A. (2010). Semantic processing in the anterior temporal lobes: A meta-analysis of the functional neuroimaging literature. *Journal of Cognitive Neuroscience, 22*(6), 1083-1094.

Wakana, S., Jiang, H., Nagae-Poetscher, L. M., van Zijl, P. C. M., & Mori, S. (2004). Fiber Tract–based Atlas of Human White Matter Anatomy1. *Radiology, 230*(1), 77-87. doi: 10.1148/radiol.2301021640

Warrington, E. K., & McCarthy, R. (1983). Category specific access dysphasia. *Brain, 106*, 859-878.

Zhong, Y.-M., & Rockland, K. S. (2003). Inferior Parietal Lobule Projections to Anterior Inferotemporal Cortex (Area TE) in Macaque Monkey. *Cerebral Cortex, 13*(5), 527-540. doi: 10.1093/cercor/13.5.527

**Acknowledgments:**

**Fig. 1**. Contrast and conjunction analysis of category-specific activations for animal and manmade objects from ALE meta-analysis. The red dots in slice views indicate the location of ROIs used in the following probabilistic tractography analysis on diffusion-weighted images.

**Fig. 2.** White-matter connectivity of the cortical semantic network for representing animal and manmade objects from probabilistic tractography. (A) Group-averaged tractography of intratemporal and occipito-temporal connectivity involving vATL, lateral and medial pFG and MOG. (B) Group-averaged tractography of parieto-temporal connectivity involving pMTG and IPL. (C) Group-averaged tractography of parieto-temporal connectivity involving medial pMTG and SPL. (D) Connectivity matrix of probability index for the ventral and IPL dorsal network (informed by functional data). The size of dots in each cell denotes the value of probability of connectivity from seed ROIs (rows) to target ROIs (columns). Only those survived from our two-level thresholding (exceeds 1% at least in half of the participants) were additionally noted with a red number (**bold** = 5% thresholding; *italic* = 2.5%; *italic* = 1%). For example, the number 0.425 in row 2 and column 4 shows that the probability of streamlines coming out from lateral pFG heading into medial pFG. (E) Connectivity matrix of probability index for the SPL dorsal network (structural data-driven).

**Fig. 3.** The summary of the cortical semantic network revealed in our ALE meta-analysis and probabilistic tractography (A) and the architecture of the neuro-computational model designed to reflect the anatomical structure of the semantic network (B). The red letters in (B) indicate the loci of lesion applied when simulating the four patterns of semantic impairments in Figure 4D-G. Green “S” for semantic dementia, red “H” for Simplex Herpes Virus Encephalitis; blue “T” for lateral parietal tumor patients; and orange “P” for pure alexia.

**Fig. 4.** Model simulation results for category-specific activation in both sighted and congenitally blind individuals and semantic impairment in four patient groups. (A-B) Unit activations in pFG, pMTG, IPL, and SPL in models trained with visual representations and tested (A) when visual representations of objects were provided as input or (B) name representations of objects were provided as input; and (C) unit activations in models trained without visual representations and tested with name representations were provided as inputs. (D-G) The accuracy of naming animal or manmade objects from the sighted models when disruptions were applied to different loci of the model to account of semantic dementia (D), Herpes Simplex Virus Encephalitis (E), lateral parietal tumor patients (F), and pure alexia (G). The line graphs show how naming accuracy declines as a function of level of severity (proportion of connections preserved), and the bar graphs show the direct comparison between the model data (averaged across all lesion levels) and patient data from previous literature. (H-I) The tendency of category related impairments (measured as naming accuracy of animal concepts minus manmade objects) associated with the lesion severity in model (H) and patient (I). The regression function and R2 are represented in corresponding color.

**Fig. 5.** A summary of our general framework for working back and forth between neuroimaging, both functional and structural, and computational techniques to understand the architecture and function of brain network.

Supplementary Materials:

Materials and Methods

Figures S1-S2

**Table S1.** Conjunction and contrast analysis of animal and manmade effects in ALE meta-analysis.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cluster | Hemisphere | | Region (Brodmann's area) | Weighted Center (x, y, z) in MNI | | | Volume (mm3) | | | ALE Statistics ( × 10-3) | |
| Conjunction | | |  |  |  | | |  |  |  |
| 1 | | Left | Fusiform gyrus (BA 19/37) | -35 | -53 | -13 | 1120 | | | 13.4 |
| 2 | | Left | Fusiform gyrus (BA 19/37) | -47 | -62 | -10 | 440 | | | 12.8 |
| 3 | | Left | IFG (BA 9/44) | -52 | 9 | 22 | 200 | | | 9.5 |
| 4 | | Right | Fusiform gyrus (BA 37) | 38 | -53 | -14 | 192 | | | 11.6 |
|  | |  |  |  | | |  | | |  | |
| Cluster | | Hemisphere | Region (Brodmann's area) | Weighted Center (x, y, z) in MNI | | | Volume (mm3) | | | ALE Statistics | |
| Animal vs. manmade | | |  |  |  |  |  | | |  |
| 1 | Left | | MOG (BA 18) | -39 | -83 | 0 | 704 | | | 2.95 |
| 2 | Right | | Fusiform gyrus (BA 20/37) | 46 | -55 | -19 | 2672 | | | 3.89 |
| 3 | Right | | STS/MTG (19/39) | 57 | -57 | 18 | 880 | | | 3.24 |
| 4 | Right | | Fusiform gyrus (BA 19) | 46 | -78 | -6 | 632 | | | 3.89 |
| Manmade vs. Animal | | |  |  |  |  |  | | |  |
| 1 | Left | | MTG/ITG (BA 37) | -53 | -61 | 0 | 2336 | | | 3.89 |
| 2 | Left | | Fusiform gyrus (BA 37) | -23 | -44 | -15 | 920 | | | 3.35 |
| 3 | Left | | IPL/Supramarginal gyrus (BA 40) | -40 | -36 | 46 | 384 | | | 3.29 |
| 4 | Right | | Fusiform gyrus (BA 37) | 27 | -50 | -13 | 1400 | | | 3.35 |

**Table S2**. Connectivity matrix of probabilistic tractography results with functional data-driven ROIs.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | From (seed regions) | | | | | | | | | | |
|  | |  | ATL | FG\_lat | MOG | | FG\_med | | MTG | | IPL\_1 | IPL\_2 | |
| MNI coordinates  (x, y, z) | | | -39, -18, -30 | -40, -54, -13 | | -39, -83, 0 | | -20, -40, -13 | | -47, -52, -4 | -40, -38, 41 | | -49, -44, 48 |
| To (target regions) | ATL | | **1.000** | **0.095** | 0.009 | | **0.131** | | 0.028 | | 0.000 | 0.001 | |
| FG\_lat | | **0.100** | **1.000** | *0.035* | | **0.425** | | ***0.042*** | | 0.001 | 0.001 | |
| MOG | | 0.011 | *0.042* | **1.000** | | 0.036 | | 0.011 | | 0.000 | 0.000 | |
| FG\_med | | **0.149** | **0.428** | *0.046* | | **1.000** | | 0.010 | | 0.000 | 0.000 | |
| MTG | | ***0.060*** | **0.082** | 0.017 | | *0.016* | | **1.000** | | *0.025* | **0.233** | |
| IPL\_1 | | 0.000 | 0.000 | 0.000 | | 0.000 | | 0.001 | | **1.000** | **0.619** | |
| IPL\_2 | | 0.000 | 0.000 | 0.000 | | 0.000 | | *0.034* | | **0.711** | **1.000** | |

*Notes*: numbers in each cell represents the group-averaged probability (maximum streamline value / 15,000) from a seed region (columns) to a target region (rows). For example, 0.428 in the 2nd column and 4th row represents the probability for connectivity from lateral fusiform gyrus to medial fusiform gyrus. ATL = anterior temporal lobe; FG\_lat = lateral fusiform gyrus; MOG = middle occipital gyrus; FG\_med = medial fusiform gyrus; MTG = middle temporal gyrus; IPL = inferior parietal lobule. *Italicized* numbers: threshold > 1% in more than 12 participants; ***Bold*** numbers: threshold > 2.5%; **Bold** numbers: threshold > 5%.

Table S3. Connectivity matrix of probabilistic tractography results with structural data-driven ROIs.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | From (seed regions) | | | |
|  |  | PHG | FG\_med | SPL\_1 | SPL\_2 |
| MNI coordinates | | -23, -18, -24 | -25, -44, -16 | -25, -51, 58 | -24, -61, 55 |
| To (target regions) | PHG | **1.000** | **0.164** | 0.006 | 0.003 |
| FG\_med | **0.076** | **1.000** | 0.000 | 0.000 |
| SPL\_1 | 0.004 | 0.000 | **1.000** | **0.669** |
| SPL\_2 | 0.002 | 0.000 | **0.658** | **1.000** |

*Notes*: numbers in each cell represents the group-averaged probability (maximum streamline value / 15,000) from a seed region (columns) to a target region (rows). PHG = parahippocampal gyrus; FG\_med = medial fusiform gyrus; SPL = superior parietal lobe. ***Bold*** numbers: threshold > 2.5%; **Bold** numbers: threshold > 5%.

References (*##-##*)

Supplementary Materials:

This section includes the actual text of the Supplementary Materials, which can include any or all of the preceding items, and figure captions and tables that can easily be incorporated into one supplementary material file. Please edit the list above as appropriate and include it at the end of your main paper. If there are additional files that cannot be easily accommodates (e.g., movies or large tables), please include captions here.

**Materials and Methods:**