Précis of White matter connectivity explains category-specific brain activation and impairment: A neurocomputational model of semantic cognition

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Abstract | To make sense of and interact with this world, human needs to accomplish a fundamental but sophisticated task: establishing a complex system, usually referred as conceptual/semantic knowledge system, that works closely with sensory and motor modalities and provides relatively coherent representations of objects, symbols, events and concepts we encounter in everyday life. One central aspect of scientific research thus focuses on understanding the cortical structure and cognitive function of such semantic system. The importance of this research topic comes from both theoretical and methodological aspects that greatly impact cognitive science, system neuroscience, and computational science. In the past few decades, different proposals have been raised to characterize the organizational principles of this knowledge system, but they diverge from each other on fundamental grounds and impose difficulties for a settlement. Furthermore, researchers have approached this question by using behavioral studies on healthy participants and brain-damaged patients, functional and structural neuroimaging, and computational models. However, a unified framework is absent to bridge findings revealed from different methods. Therefore, this dissertation aimed to provide a novel neurocomputational framework of semantic cognition to reconcile the theoretical discrepancies from different tenets as well as to propose a research approach that integrates multiple methods.

1 Introduction

Research into the cognitive and neural bases of semantic knowledge system in human brain has long focused on an intriguing phenomenon first reported in the early 1980's (Warrington & McCarthy, 1983; Warrington & Shallice, 1984): following brain injury, some patients appear to lose their knowledge about some semantic categories while knowledge of other categories remains relatively preserved or even normal (Gainotti & Silveri, 1996; Garrard, Lambon Ralph, Hodges, & Patterson, 2001). In many cases, this category-specific pattern persists even when obvious confounding factors are controlled; across patients the affected categories can doubly dissociate; and there are reliable associations between lesion location and the categories affected.

Efforts to understand the implications of category-specific deficits for the cognitive and neural organization of the semantic system have been caught between two polar proposals. The first claims that the semantic system is _modular and domain-specific_: anatomically distinct and functionally independent neural systems have evolved to support knowledge about different conceptual domains (e.g. animals, tools, people, body-parts, scenes, emotions, etc.; Kanwisher, 2010; Mahon & Caramazza, 2009). The second argues that the cortical semantic system is _interactive and domain-general_: all concepts are encoded in a distributed network that allows human beings to learn the high-order perceptual, motor, and linguistic structure of their environment in order to make effective inferences about new objects, situations, and statements in daily life (Lambon Ralph, Sage, Jones, & Mayberry, 2010; Rogers et al., 2004; Warrington & McCarthy, 1987). Supporting evidence for the second view comes from studies of semantic dementia (SD), a progressive disorder characterized by degeneration of both verbal and nonverbal semantic knowledge and bilateral neuropathology focused on the anterior temporal lobes (ATL; Lambon Ralph et al., 2007). Patients with SD essentially show a global semantic impairment that affects different semantic categories equally, so long as other confounding

factors are controlled. Though these proposals have profoundly different implications about the roots of human cognition (Martin, 2007), neither proposal accounts for the wide spectrum of semantic deficits, from category-specific to domain-general, across different types of neuropathology.

The debate has extended into the arena of neuroimaging since seminal studies showing that functional activation in certain brain regions are sensitive to semantic categories (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995). These patterns were quickly taken as supporting evidence for the domain-specific view (Caramazza & Mahon, 2003; Kanwisher, McDermott, & Chun, 1997). Later investigations, however, have suggested that category-sensitive patterns, especially in the ventral visual stream (e.g., posterior FG), may be driven by perceptual or experiential confounds (Gauthier, Skudlarski, Gore, & Anderson, 2000; Mechelli, Sartori, Orlandi, & Price, 2006). The picture was further complicated by the recent finding that congenitally blind individuals show _quantitatively similar_ as well as _qualitatively different_ patterns of category-sensitive activation in both ventral and dorsal visual streams (Bedny, Caramazza, Pascual-Leone, & Saxe, 2012; Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009; Mahon, Schwarzbach, & Caramazza, 2010). Thus functional brain imaging, though providing an important source of evidence, still does not adjudicate domain-specific and domain-general accounts, but simply adds more puzzles for both sides to explain.

Researchers embracing the domain-general view have employed computational models to demonstrate how an interactive and unified system can account for both category-specific and domain-general deficits. Such work has shown that category-specific deficits can arise from graded functional specialization in the semantic system driven either by differential reliance on sensory versus functional properties of objects (Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Farah & McClelland, 1991) or from evolutionary pressure to utilize short, local connections (Plaut, 2002). The global deterioration of semantic knowledge in SD has also been modeled as arising from lesions in cross-modal semantic representations coded in the ATL (Rogers et al., 2004). The same model was later shown to explain both domain-general and category-specific deficits as arising from different forms of pathology to ATL in SD and Herpes Simplex Virus Encephalitis (HVSE; Lambon Ralph, Lowe, & Rogers, 2007). These models offered concrete mechanisms for understanding semantic deficits in various syndromes, but shed little light into the cortical organization of the semantic network and do not readily explain the findings from functional neuroimaging. Also, the explanations of semantic deficits provided by these models are slightly different from each other despite generally embracing a domain-general perspective. Thus, a unified theoretical framework is needed to explain the full range of neuroimaging findings and of the different patterns of semantic deficits caused by various neuropathologies.

In this dissertation, I propose a new framework, the "base connectivity hypothesis", that bridges domain-specific and domain-general approaches by emphasizing the important role of network connectivity, in addition to learning and environmental structure, in shaping the ultimate functioning and response profiles of different network components. I argue that the function and organization of the semantic system are constrained by both the anatomical structure of the cortical semantic network and by the statistical structure of learning experiences across multiple modalities. Like other views, the base connectivity hypothesis (hereafter, BCH) assumes that semantic memory functions to promote effective inferences about important but unobserved states of affairs in the world. Effective inferences are computed via learned associations among various modality-specific _surface representations_: perceptual, linguistic, and action representations coded in different regions throughout cortex.

BCH differs from previous views (Caramazza & Shelton, 1998; Tyler & Moss, 2001; Warrington & Shallice, 1984) in emphasizing the importance of anatomical connectivity for understanding how components of the semantic network operate and the functional responses they exhibit (Binney, Parker, & Lambon Ralph, 2012; Chen & Rogers, 2015; Gomez et al., 2015; Mahon & Caramazza, 2011; Mesulam, 1998; Plaut & Behrmann, 2011). Pathways connecting various surface representations in the

network are assumed to differ in their strength or effectiveness. Regions that are robustly connected exert strong mutual influences and so respond similarly to given inputs. The activation patterns generated within such network by a given stimulus thus reflect, not only the effects of learning in a structured environment, but also the base connectivity of the network. Because items from different conceptual domains vary systematically in the surface representations they engage (Cree & McRae, 2003; Warrington & Shallice, 1984)—with, for instance, tools more often engaging action representations and animals more often engaging movement representations—the joint effects of learning and connectivity can lead some cortical regions to contribute more to the representation of some conceptual domains, consistent with the distributed domain-specific hypothesis (Mahon & Caramazza, 2009, 2011). Yet these effects arise through domain-general learning of environmental structure, and network components that are centrally connected remain critical for representation and processing of items from all conceptual domains, consistent with the domain-general view (Chen & Rogers, 2015; Pobric, Jefferies, & Lambon Ralph, 2010).

The BCH reflects recent ideas from several groups that investigate how neural structure, either functional or anatomical, constrains cortical functions (Gomez et al., 2015; Sadtler et al., 2014). Recent evidence from brain imaging (Gomez et al., 2015; Mahon et al., 2007) and computational modeling (Chen & Rogers, 2015; Plaut, 2002) establishes the face validity of its central tenet. Yet the potential of BCH to provide a unifying account of semantic representation remains untested. While many studies have employed functional imaging or lesion-symptom correlation to identify brain regions involved in semantic processing (Damasio et al., 1996; Martin et al., 1995), few simultaneously consider neural connectivity or specify how the identified regions contribute to healthy and disordered semantic processing. Studies examining connectivity and function together (Gomez et al., 2015; Mahon et al., 2007; Plaut & Behrmann, 2011) have focused on individual network subcomponents at the expense of understanding its whole functioning. Neurocomputational models have advanced explicit proposals about how connectivity could shape representation and functioning in healthy and damaged networks (Plaut, 2002; Rogers et al., 2004), but with little reference to functional activation and connectivity measured in real brains. One consequence of this disconnection across studies is that specific proposals about the neural bases of semantic representation remain at odds in many of their core claims even amongst researchers who generally accept the importance of connectivity in shaping semantic representation (e.g., Chen & Rogers, 2015; Mahon & Caramazza, 2011; Plaut & Behrmann, 2011).

2 Summary of the dissertation

From the introduction, we can see that three major gaps exist in the literature of semantic cognition: (a) existing domain-specific and domain-general views have difficulties to explain the wide range of findings studies on both healthy and impaired brain; (b) computational models need to provide a unified framework to explain the origin of normal and disrupted representations and functions of the cortical semantic network; and (c) to understand semantic representation in the brain, we need first to understand the large-scale connectivity of the cortical network for semantic cognition. In my dissertation, I integrated functional brain imaging, probabilistic tractography, behavioral neuropsychology, and neurocomputational modeling to assesses whether the BCH offers a unified account of healthy and disordered semantic representation in the brain. From prior work and a new ALE meta-analysis of functional imaging studies, I first delineated cortical regions involved in semantic representation and identified those showing reliable category-sensitive effects. I then established the long-range connectivity amongst these regions through probabilistic diffusion-weighted tractography, providing the first characterization of the large-scale anatomical structure for the cortical semantic network. From these results, I constructed a recurrent neural network model whose architecture conformed to the results of the tractography. My central question then was whether such an

anatomically-constrained model, after learning, explains the primary sources of evidence adduced in support of both domain-specific and domain-general theories—specifically, patterns of functional activation observed in brain imaging studies of semantics, patterns of impairment observed in the primary disorders of semantic representation, and the anatomical bases of these disorders.

2.1 Cortical semantic network revealed by ALE meta-analysis and literature

I carried out an ALE meta-analysis (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012) of previous functional neuroimaging studies to find regions showing reliable category-sensitive activations. Combining these results with a review of related literature, I mapped out a cortical semantic network for both modality-specific and cross-modal semantic representation. The contribution of this work is two-fold. First, the ALE meta-analysis provides the largest review and meta-analysis of neuroimaging studies for category-sensitive activations associated with different stimuli types and cognitive tasks. Second, this work identified critical regions of the cortical semantic network and specified which regions reliably exhibit category-sensitive activation patterns across tasks. These results then informed the subsequent tractography study, ultimately leading to both the architecture of the neurocomputational semantic model and the imaging data such a model must explain.

Based on 54 papers with a total number of 73 studies (31 for animal and 42 for artifact) and 270 foci (103 for animal and 167 for artifact), the ALE meta-analysis revealed the following results (see Figure 1A). The medial aspects of _posterior FG_ activated more for artifacts than animals bilaterally, while the lateral aspect activated more for animals. The differential engagement of lateral and medial pFG for animals and artifacts is well documented and typically thought to be bilateral (Martin & Chao, 2001). Artifacts also produced significantly greater activation than animals in _lateral parietal cortex (LPC)_ with a cluster spanning inferior and superior lobules, which patient and imaging literatures suggest encode different aspects of action knowledge (Binkofski & Buxbaum, 2013). Greater activation for artifacts was observed in _posterior MTG_, a region implicated in the semantic representation of tools(Martin, 2007). _Lateral occipital cortex (LOC)_ was activated more for animals than artifacts, likely reflecting domain differences in visual structure including greater complexity and more overlap among animals relative to manmade objects (Humphreys & Riddoch, 2006).

In combination with the literature review, I identified medial and lateral _pFG_, superior and inferior _LPC_, and posterior _MTG_ from as regions of interest in the cortical semantic network. I further considered LOC as a source of visual input to infero-temporal cortex, with the further assumption that animal have richer and more overlapping visual structure than artifacts in this region (Humphreys & Forde, 2001) I also identified two regions important in the literature review but not revealed in the meta-analysis: _Ventral ATL,_ whose importance to semantic representation has been established by converging evidence from patient studies, brain imaging with appropriate methodology, transcranial magnetic stimulation and lesion-symptom mapping; and _superior temporal gyrus (STG)_ which did not show reliable category-sensitive effects, but has a well-known role in encoding spoken word forms including animal and artifact names.

2.2 Connectivity of the cortical semantic network from probabilistic tractography

In this section of the dissertation, I examined connectivity patterns within cortical semantic network delineated in the previous analysis. Several recent studies demonstrate that abnormality in white matter fibers is associated with semantic dysfunction for some patient groups (Acosta-Cabronero et al., 2011; Han et al., 2013). For instance, Noppeney et al. (2007) showed that patients with SD and HSVE had significant decrease in white matter volume in bilateral ATL. Probably the most convincing evidence comes from a study showing that intraoperative direct simulation of several white-matter fibers in the temporal lobes resulted in anomia, semantic and phonological paraphasia (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007). And of course, the BCH proposes that graded

functional specialization partly arises from underlying network connectivity. Measuring the connectivity thus constitutes a critical step toward testing the BCH, and also will allow me to assess how disruption to connectivity in different network components might disrupt semantic processing.
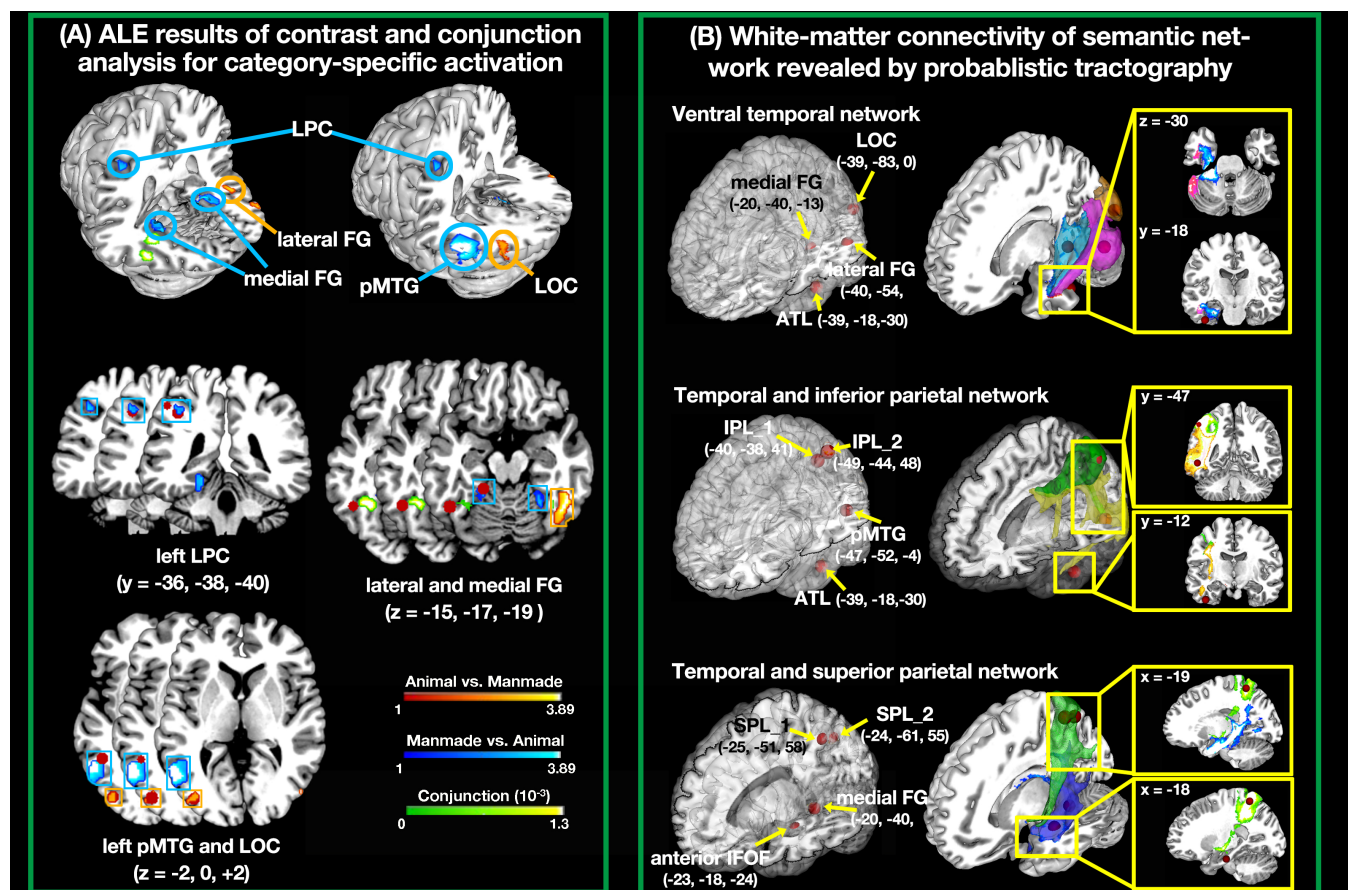
Figure 1. Cortical semantic network revealed by ALE meta-analysis and probablistic tractography. (A) Red dots showed ROI seeds used in tractography analysis; (B) ROI seeds were chosen based on ALE analysis and previous literature. Top: cyan showed streamlines from medial FG, and purple showed those from lateral FG; Middle: yellow for pMTG streamlines and green for IPL streamlines; Bottom: green for SPL and blue for IFOF streamlines.

Streamline-based probabilistic tractography analysis (Parker & Alexander, 2005) was conducted based on diffusion-weighted images from 24 participants using methods optimized to reduce the susceptibility artifact in ventral ATL. I focused on examining the connectivity patterns between seed regions from ALE analysis or the literature noted in previous section. STG was excluded from the analysis since its connectivity is well-studied(Binney et al., 2012). The major findings of tractography analysis can be summarized as three subnetworks (see Figure 1B). _Ventral temporal network_: both lateral and medial pFG showed highly probable connections projecting into ATL and to one another. ATL also projected to both pFG regions and to the pMTG. Streamlines from pMTG terminated in the ATL seed and projected to lateral pFG with high probability and to medial pFG with moderate probability. _Temporal and inferior parietal network_: streamlines from the ATL did not extend into parietal cortex. Streamlines from pMTG, however, projected both to ATL and to the inferior aspect of LPC, providing an indirect route from LPC to the ATL via pMTG. Likewise, the LPC streamlines projected to pMTG but not to ATL. _Temporal and superior parietal network_: medial pFG did not stream to LPC, but did project more superiorly within the parietal lobe, possibly reflecting the dorsal branching structure of the inferior longitudinal fasciculi (ILF) observed in non-human primates. If present, this pathway potentially connects ATL to superior LPC regions via the medial pFG. To test this possibility we placed an anterior seed in the medial pFG cluster and assessed its posterior trajectory. The streamline passed through the medial pFG neighborhood and branched superiorly into LPC. Likewise, streamlines placed in superior LPC descended to intersect the IFOF streamline. Thus the

tractography reveals two pathways from temporal to parietal regions of the network: one that connects ATL to the more inferior region via the pMTG, and a second connecting ATL to the more superior region via the medial pFG. To my knowledge this is the first identification of the posterior temporo-parietal tract using probabilistic tractography, though similar pathways have been observed in human dissection and in tracing studies with non-human primates. The principal contribution of this part of this dissertation is the first large-scale characterization of the anatomical connectivity of the cortical network for semantic representation.

2.3 Anatomically constrained model explains category-sensitive activation

While prior models have successfully explained healthy and dysfunctional performance on semantic tasks, no prior model has sought to explain functional imaging data in semantic studies. In this chapter I utilized the information from ALE analysis and probabilistic tractography to establish the architecture of a neural network model. I then trained the model and assessed whether it could explain the category-specific patterns of activation revealed in the ALE analysis.

A fully recurrent neural network of semantic knowledge was constructed and trained to compute mappings among distributed representations of objects across different modalities (Figure 2A). External inputs were applied to four visible layers to capture the statistical structure of feature distributions across different modalities for both animal and artifact concepts. The model was trained with predictive error-driven learning to generate an item's full complement of visual (LOC), verbal (STG), function (inferior LPC; IPL) and praxis (superior LPC; SPL) properties, given a subset of these as input. Modality-specific surface representations were generated to capture three well-documented aspects of environmental structure: (1) hierarchical similarity with few properties shared across domains, more shared within domains, and many shared within basic categories, (2) many more praxic and functional features for artifacts and more visual features for animals, and (3) more feature overlap amongst animals than artifacts. Models were tested with simulations of both auditory word and visual picture comprehension. Units in hidden layers were given fixed negative bias weights so that, in the absence of input, they adopted low activations. Activation patterns generated by word or image inputs were then treated as analogs of the BOLD response in corresponding fMRI tasks.

All category-sensitive effects observed in the ALE analysis emerged in the corresponding model layers for both word and picture stimuli (see Figure 2B). Specifically, medial pFG, pMTG, IPL and SPL responded more to artifacts because they strongly interact with function or praxis representations, which are rich for artifacts. Lateral pFG responded more to animals because the medial units had "specialized" to represent artifacts. Thus, model connectivity, learning and environmental structure together produced the category-sensitive activations observed in the ALE analysis. I next simulated the category-sensitive activations in congenitally blind participants during word comprehension by assessing models trained without visual inputs and targets. Just as in blind participants, the model showed no animal advantage in lateral pFG (*qualitative difference* from the sighted), presumably because these units no longer communicate activation from early vision. Artifacts, however, continued to elicit greater activation in medial pFG, pMTG, IPL, and SPL (*quantitative similarity* to the sighted), because these units continue to participate in generating function and praxis representations for object-directed action. This model is the first to account for the full range of reliable category-specific functional activation patterns in functional brain imaging.

2.4 Anatomically-constrained model explains patterns of semantic impairment

In the final chapter I tested whether the same model also explains patterns of semantic impairment observed across three well-documented syndromes: SD, which produces global and severe semantic impairment across categories (Hodges, Patterson, Oxbury, & Funnell, 1992); HSVE, which produces more severe knowledge deficits for animals than for artifacts (Lambon Ralph et al.,

2007); and tumor resection in posterior temporo-parietal cortex (TP_Tumor), which produces a small but systematic disadvantage in naming artifacts compared to animals (Campanella, D'Agostini, Skrap, & Shallice, 2010).

Using the same architecture, trained models were lesioned in three different manners to account for the three patterns of semantic deficits. For SD, all connections coming in and out of the ATL layer were randomly pruned. For HVSE, connections between lateral units of pFG and ATL were randomly pruned. For TP_Tumor, connections between pMTG and IPL were randomly pruned. The same lesion procedure was applied for all three cases, and lesion sites were selected based on existing knowledge of disrupted white-matter tracts associated with each disorder (Acosta-Cabronero et al., 2011; Campanella et al., 2010; Noppeney et al., 2007). The model performance was assessed by a procedure analogous to picture naming in which the models produced item names with only visual inputs provided.

The model captures the direction and magnitude of several key phenomena including (see Figure 2C): (1) no category effect in SD, (2) a substantial and large animal disadvantage in HSVE, and (3) a modest artifact disadvantage in TP_Tumor. Network connectivity transparently explains the interesting patterns for all three syndromes: ATL damage produces a domain-general impairment for SD; removal of lateral ATL-pFG connections produced profound animal disadvantage like HSVE, for these connections provide more support for animal knowledge. Disruption of pMTG and IPL connections like resection for TP_Tumor, disturbed representations of functional knowledge that were more important for artifacts. In sum the model suggests an account of semantic disorders in which network connectivity, learning, and environmental structure all play critical roles. Furthermore, lesion-symptom correlation analysis revealed the relationship between lesion severity and behavioral performance in the model was quite similar to empirical data from patients. Also, the overall pattern of larger category-specific impairment to animal concepts compared with artifacts reflected the pattern revealed by a review of reported single-case studies. This is the first model in the literature to provide
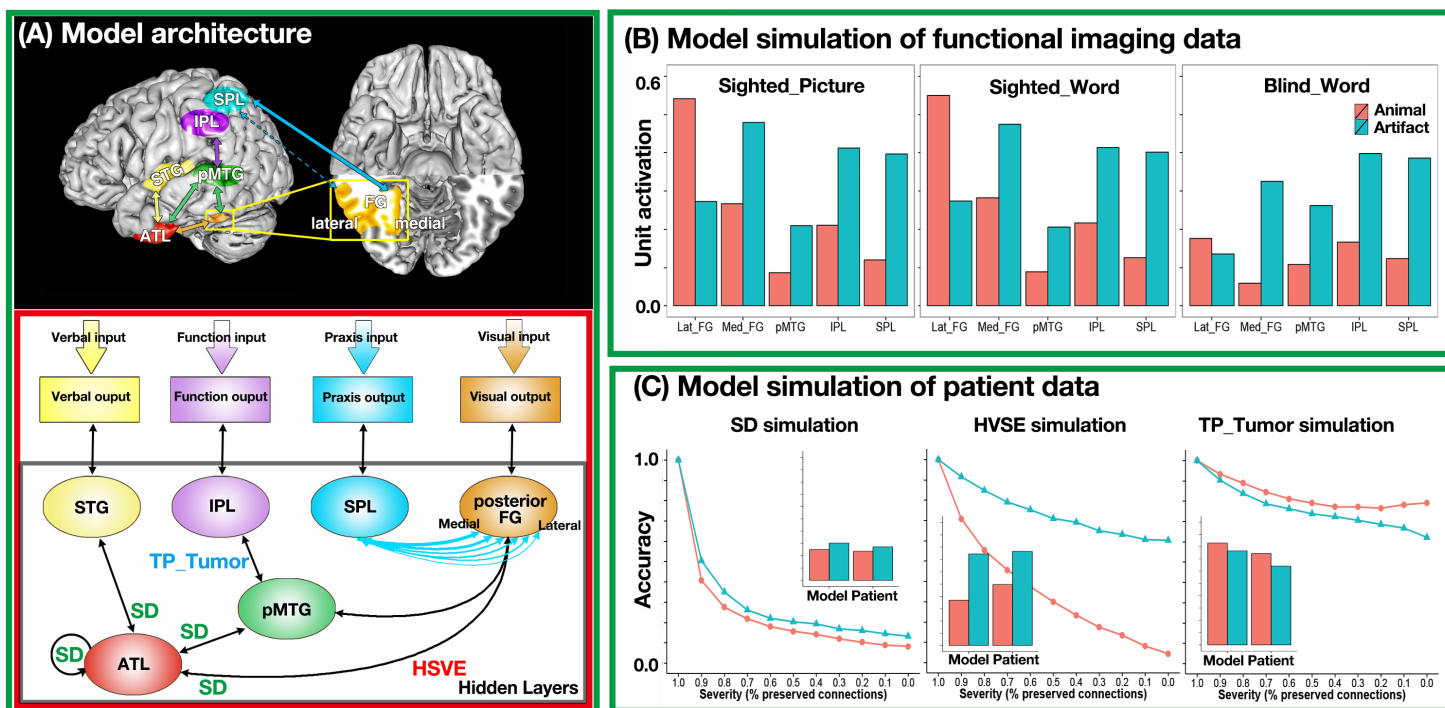

Figure 2. Neurocomputational model for semsntic cognition. (A) Summary of cortical semantic network and model architecture. In the bottom panel, SD (green), HSVE (red), and TP_Tumor (blue) showed the sites of connections affected to simulate corresponding pathology; **(B)** Simulations of observed category-sensitive activations in sighted and congenitally blind in picture and word comprehension tasks; **(C)** Simulations of picture naming accuracy for SD, HSVE and TP_Tumor patients. Line graphs show the relationship between lesion severity and behavioral performance, and bar graphs show averaged model performance compared to patient data from previous studies (SD and HVSE: Lambon Ralph et al., 2007 and Noppeney et al, 2007; TP_Tumor: Campanella et al., 2010).

an account of domain-general semantic impairment in SD as well as both sides of the category-specific double-dissociation that motivates domain-specific accounts.

3 Conclusions and interdisciplinary contributions of this dissertation

This dissertation makes important contributions to cognitive science, systems neuroscience and computational science, and could not have been completed from any of these domains individually. First, the ALE meta-analysis and probabilistic tractography together delineate a distributed cortical semantic network encompassing regions in occipital, temporal and parietal cortices, and establish both the connectivity among these regions and their response profiles. The general approach of using meta-analytic functional imaging results to seed connectivity analyses is novel to my knowledge, and provides a roadmap for similar work in any other representational domain. Second, the neurocomputational work presented in this dissertation is the first to explain category-sensitive functional activation patterns in healthy populations, and the first to show how such patterns can arise in congenitally blind participants. This work also demonstrates the potential of neural network models to simulate and explain data from functional neuroimaging, providing a conceptual bridge between computational and neuroimaging approaches to cognition. Third, the same neurocomputational model is the first to explain both category-specific and domain-general patterns of semantic deficits arising from different types of pathology. By lesioning connections at different sites within the same network, the model provided simple explanations for a diversity of phenomena in the neuropsychology of semantic memory. Fourth, the proposed base connectivity hypothesis bridges previously irreconcilable views of semantic cognition by illustrating how neural connectivity, learning, and cross-modal environmental structure work together to shape functional properties of the network. This proposal facilitates the shift from time-worn debates between domain-specific and domain-general views to more fruitful investigations of what and how functional and anatomical structures constrain the cognitive functions of cortical regions. Last but not least, this dissertation illustrates a novel way of integrating behavioral, functional and structural imaging, computational modeling and neuropsychological methods iteratively, which can be readily applied to other domains to characterize the common and unique properties of different neurocognitive networks.

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