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# Neural Mechanisms for Combinatorial Semantics in Language and Vision: Evidence From FMRI, Patients, and Brain Stimulation

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# Neural Mechanisms for Combinatorial Semantics in Language and Vision: Evidence From fMRI, Patients, and Brain Stimulation

## **Abstract**

Throughout our daily experience, humans make nearly constant use of semantic knowledge. Over the last 20-30 years, the majority of work on the neural basis of semantic memory has examined the representation of semantic categories (e.g., animate versus inanimate). However, a defining aspect of human cognition is the ability to integrate this stored semantic information to form complex combinations of concepts. For example, humans can comprehend “plaid” and “jacket” as separate concepts, but can also effortlessly integrate this information to create the idea of a “plaid jacket.” This process is essential to human cognition, but little work has examined the neural regions that underlie conceptual combination. Many models of semantic memory have proposed that convergence zones, or neural hubs, help to integrate the semantic features of word meaning to form coherent representations from stored semantic knowledge. However, few studies have specifically examined the integrative semantic functions that these high-level hub regions carry out. This thesis presents three experiments that examine lexical-semantic combinatorial processing (as in the “plaid jacket” example above): 1) a study in healthy adults using fMRI, 2) a study in healthy adults using brain stimulation, and 3) a study examining impairments of lexical-semantic integration in patients with neurodegenerative disease. The fourth and final experiment of this thesis examines semantic aspects of combinatorial codes for visual-object representation. This study identifies neural regions that encode the feature combinations that define an object’s meaning. The findings from these four experiments elucidate specific cortical hubs for semantic-feature integration during language comprehension and visual-object processing, and they advance our understanding of the role of heteromodal brain regions in semantic memory.

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NEURAL MECHANISMS FOR COMBINATORIAL SEMANTICS IN LANGUAGE AND VISION:  
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Amy Rose Price

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in

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## ABSTRACT

Throughout our daily experience, humans make nearly constant use of semantic knowledge. Over the last 20-30 years, the majority of work on the neural basis of semantic memory has examined the representation of semantic categories (e.g., animate versus inanimate). However, a defining aspect of human cognition is the ability to integrate this stored semantic information to form complex combinations of concepts. For example, humans can comprehend “plaid” and “jacket” as separate concepts, but can also effortlessly integrate this information to create the idea of a “plaid jacket.” This process is essential to human cognition, but little work has examined the neural regions that underlie conceptual combination. Many models of semantic memory have proposed that convergence zones, or neural hubs, help to integrate the semantic features of word meaning to form coherent representations from stored semantic knowledge. However, few studies have specifically examined the integrative semantic functions that these high-level hub regions carry out. This thesis presents three experiments that examine lexical-semantic combinatorial processing (as in the “plaid jacket” example above): 1) a study in healthy adults using fMRI, 2) a study in healthy adults using brain stimulation, and 3) a study examining impairments of lexical-semantic integration in patients with neurodegenerative disease. The fourth and final experiment of this thesis examines semantic aspects of combinatorial codes for visual-object representation. This study identifies neural regions that encode the feature combinations that define an object’s meaning. The findings from these four experiments elucidate specific cortical hubs for semantic-feature integration during language comprehension and visual-object processing, and they advance our understanding of the role of heteromodal brain regions in semantic memory.

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## CHAPTER 1

Nothing, at first view, may seem more unbounded than the thought of man, which not only escapes all human power and authority, but is not even restrained within the limits of nature and reality. To form monsters, and join incongruous shapes and appearances, costs the imagination no more trouble than to conceive the most natural and familiar objects.... But though our thought seems to possess this unbounded liberty, we shall find, upon a nearer examination, that it is really confined within very narrow limits, and that all this creative power of the mind amounts to no more than the faculty of compounding, transposing, augmenting, or diminishing the materials afforded us by the senses and experience.

David Hume, 1777

## INTRODUCTION

Memory allows us to capture information from our life experiences and take advantage of this information in the future. One of the advantages of memory, as Hume observed, is that we can use it to construct a seemingly unbounded variety of thoughts in imagination. This stored knowledge about the world makes up what is known as our semantic memory. This type of memory differs from the autobiographical memory of past experiences, known as episodic memory. This observation is consistent with advances in psychology over the last half century that have taught us that not all memories are created equal. There is now a great deal of evidence that there are different kinds of memory. In this chapter, I will focus on a particular type of memory—semantic memory. I will begin by placing semantic memory within a broader context and discussing the major division between episodic and semantic memory. I will then review what is known about the cognitive and neuroanatomic architecture of the semantic memory system.

## DECLARATIVE MEMORY: EPISODIC AND SEMANTIC

At the beginning of the 20<sup>th</sup> century, memory was typically characterized as a single entity without clear-cut subdivisions. One useful distinction within the memory literature emerged in 1972 when Endel Tulving articulated a theoretical framework that discriminated between two different types of memory: episodic and semantic. Both of these types of memory are considered part of our declarative memory (also known as explicit memory), which is our memory for knowledge and events that can be consciously recalled. According to Tulving, episodic memory refers to our autobiographical memories for specific personal experiences, which depend critically on the context of the personal event. Semantic memory refers to our general knowledge about the world, including knowledge about people, places, and facts. Semantic memories are not tied to specific personal events, but instead reflect an abstraction across these specific events that captures the critical features that these events have in common. For example, remembering the experience of your last canoe trip relies on episodic memory, whereas understanding the meaning of *canoe* (I use italics to indicate a concept) relies on a distillation of the commonalities associated with all of our experiences with canoes (i.e., something like “a light, narrow, pointed boat that is paddled”).

Early neuropsychological evidence from patients with focal brain lesions supported the distinction between these two types of memory. For example, patients with lesions affecting the medial temporal lobe showed a particularly severe impairment of episodic memory but relatively intact semantic memory (Scoville and Milner, 1957; Warrington, 1975; Squire and Zola, 1998). In other words, these patients had little

trouble understanding the meaning of words and objects, but they had almost no ability to remember new events they had experienced. There also appear to be dissociations between how semantic and episodic memories are acquired. It has been shown, for example, that children who develop amnesia after incurring hippocampal damage early in life can still acquire seemingly normal semantic knowledge throughout development even though they have difficulty acquiring new episodic memories (Vargha-Khadem et al., 1997; Gardiner et al., 2008). Furthermore, it appears that patients with profound episodic memory difficulty due to Alzheimer's disease can still acquire and retain the meaning of new words and objects (Grossman et al., 2007; Murray et al., 2007).

Other work described patients with the opposite dissociation—prominent semantic memory difficulty with relatively spared episodic memory (Warrington, 1975). Subsequent studies associated this pattern of impaired semantic memory with atrophy in inferolateral and anterior portions of the temporal lobe in patients with a syndrome known as semantic dementia (now referred to as semantic variant of primary progressive aphasia, svPPA) (Mummery et al., 2000). These patients show a severe deficit in semantic memory, evident in their difficulty understanding the meaning of words and objects, but have relatively intact episodic memory (Warrington, 1975; Hodges and Patterson, 2007; Grossman, 2010; Hornberger and Piguet, 2012).

The dissociation between episodic and semantic memory provided a useful framework on which to build cognitive and neurobiological theories of human declarative memory. Early work from patients with focal brain damage led to the general conclusion that medial temporal lobe regions primarily support episodic memory, whereas lateral temporal regions primarily support semantic memory. And indeed, behavioral and neuroimaging studies in healthy subjects further indicated that these two types of

memory relied on distinct brain networks (Posner and Keele, 1968; Jacoby and Dallas, 1981; Vandenberghe et al., 1996; Cabeza et al., 1997). Nonetheless, there is still much on-going debate over the degree to which these memory systems are independent and rely on distinct neural substrates. For example, some models of hippocampal functioning posit a role for medial temporal structures in the formation of semantic memories (Love et al., 2004; Davis et al., 2012) and there is evidence implicating neocortical structures in episodic memory (Rugg and Yonelinas, 2003). With the continued development of brain imaging techniques, it has become increasingly evident that the episodic and semantic memory systems rely on partially overlapping large-scale brain networks that include not only the medial and lateral temporal lobes but also portions of the frontal and parietal lobes. Thus, although the theoretical distinction between episodic and semantic memory has proven useful in many ways and there is much evidence for gross anatomical distinctions between the two systems, at a more fine-grained anatomic level the distinctions are not as clear-cut.

In the remainder of this chapter, I will consider in greater detail how the semantic memory system is organized in the brain. Although, semantic memory encompasses a broad range of knowledge, I will focus mostly on the semantic representation of single objects and words. Indeed, many investigations of semantic memory have focused on these basic semantic representations, which lend themselves to controlled experimental investigation. I will first consider the neural and psychological perspectives for the organization of concrete semantic knowledge (i.e., knowledge about concepts that have a physical existence in the world such as knowledge about objects, people, and places) and then consider the perspectives for how abstract semantic knowledge is organized in the brain (i.e., knowledge about concepts that do not have an easily identifiable physical

existence, such as the concepts *hope*, *mercy*, and *desire*). Next, I will consider perspectives on how semantic knowledge is integrated and abstracted across concepts in the brain.

## **ORGANIZING PRINCIPLES OF SEMANTIC MEMORY**

### **Grounded Knowledge**

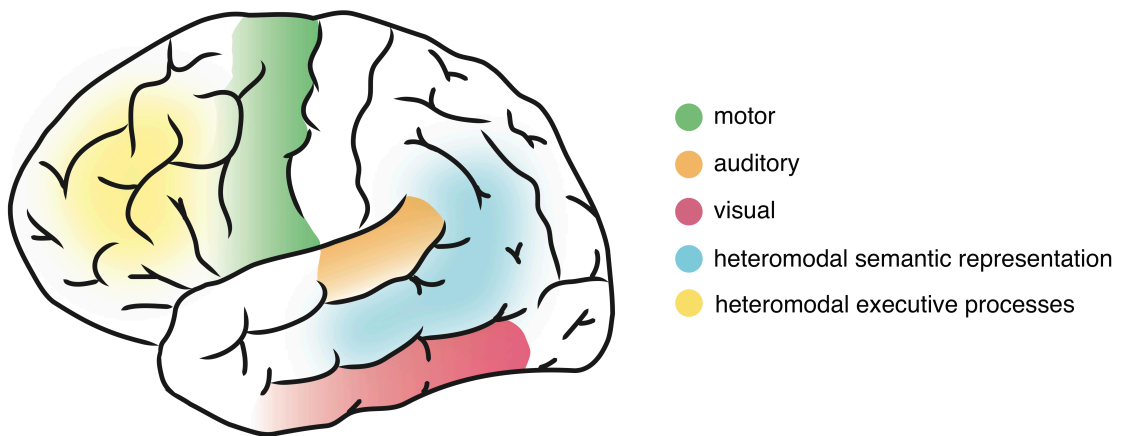
When Tulving proposed partitioning declarative memory into episodic and semantic memory, he characterized the semantic memory component as a single, amodal system in which all semantic knowledge is stored (Tulving, 1972). Alternative theories about the organization of semantic memory were subsequently proposed that contradicted this amodal framework. These proposals, originating in the neuropsychology literature, described patients with selective deficits for a single category of knowledge within semantic memory, rather than damage to the entire semantic memory network. In 1983, for example, Warrington and McCarthy described a patient with a semantic memory deficit that was worse for non-living objects (e.g., tools, furniture) than for natural kinds (e.g., animals, food, plants). The next year, Warrington and Shallice (1984) reported a group of patients with the opposite pattern of semantic impairment—worse performance on living than on non-living objects. Such semantic deficits were referred to as “category-specific.” These observations suggested that the semantic memory system is subdivided into different components based on the content of concepts. Interestingly, many other forms of category-specific semantic deficits have been reported in the literature

(Goodglass et al., 1966; Gainotti et al., 1995; Shapiro et al., 2000), such as selective impairments for color (Damasio et al., 1979) and for body parts (Dennis, 1976).

There has been much debate over how these category-specific impairments emerge. One theory proposed that semantic knowledge is organized into specific domains, such as animate (e.g., animals) and inanimate (e.g., tools, furniture), as a result of evolutionary constraints. According to this account, known as the domain-specific account, specialized neural circuitry evolved to facilitate a recognition advantage for certain categories necessary for survival (Caramazza and Shelton, 1998). These evolutionary constraints would then give rise to separate knowledge stores for specific categories. An example is the innate ability for three-month olds to distinguish between biological and non-biological motion (Bertenthal et al., 1984).

Other accounts proposed that different semantic categories rely on different sensory-motor features (Wernicke, 1900; Allport, 1985; Warrington and McCarthy, 1987; Gage and Hickok, 2005), which I refer to here as the sensory-motor account. The central idea behind sensory-motor accounts of semantic memory is that the sensory and motor feature associations of object concepts constitute the primary organizing principle in semantic memory. In this view, object concepts are composed, in part, of sensory and motor feature associations that are critical to their meaning, and these features are stored in or near the corresponding sensory and motor regions of the brain. According to this theory, semantic representations rely on distributed networks of features, and these networks parallel the anatomic distribution of the brain's sensory and motor systems. For example, the concept *hammer* has visual-perceptual features associated with it that identify its appearance, and it is hypothesized that these features are represented in ventral portions of visual association cortex. *Hammer* also has motor features associated

with how to grasp and make use of it, and it is proposed that they are represented in or near motor and premotor brain regions. Other features of *hammer* may include characteristic motion features in or near motion-perception regions of visual association cortex and auditory features, such as the pounding sound of a hammer, represented in or near auditory association cortex. This account attributes category-specific deficits to the fact that these categories have differentially weighted sensory-motor feature associations. For example, because tool concepts like *hammer* have more motor features than animal concepts like *cat*, they tend to rely more heavily on representations in motor and premotor association cortices.



**Figure 1.** Sensorimotor brain regions that are thought to support sound (orange), action (green), and visual (pink) conceptual features are illustrated in or near the primary auditory, motor, and ventral visual cortical regions, respectively. Heteromodal brain regions for representing integrated conceptual information (light blue) and heteromodal brain regions for performing executive processes (yellow) are highly interconnected to sensorimotor brain regions. Furthermore, the heteromodal regions in the frontal, temporal, and parietal cortices are also highly interconnected with each other. For illustrative purposes, we only depict the broad categories of sensorimotor features (adapted from Price et al. (2015a)).

Several lines of investigation lend support to this account. For example, patients with a neurodegenerative motor disorder known as amyotrophic lateral sclerosis (ALS) have greater difficulty naming and understanding concepts like *hammer* that are associated with motor actions (Grossman et al., 2008). Disease in auditory association cortex appears to compromise the representation of concepts such as *thunder* that depend on auditory feature knowledge more than concepts that do not have auditory feature associations (Bonner and Grossman, 2012). Natural kind concepts such as *cat* appear to rely heavily on the representation of their visual appearance and thus may be relatively vulnerable to disease in visual association cortices. In line with this, patients with Alzheimer's disease, who have a substantial neurodegenerative burden in ventral portions of visual association cortex, often have difficulty with animal concepts (Garrard et al., 2005; Garrard and Carroll, 2006; Libon et al., 2013). Findings such as these suggest that category-specific semantic deficits arise, in part, because damage to a sensory-motor association region differentially degrades the modality-specific feature knowledge associated with different semantic categories.

While both the domain-specific account and the sensory-motor account predict category-specific deficits for fundamentally different reasons, the evidence to date has provided stronger support for a sensory-motor account of semantic memory. Much of this evidence comes from functional neuroimaging studies in healthy young adults. An early functional neuroimaging study of semantic memory (Martin et al., 1995) demonstrated that the same object could evoke activation in markedly different brain regions depending on the type of feature that was being retrieved. Specifically, these researchers found that retrieving the color of an object evoked activation in ventral visual association cortices, while retrieving an action feature of the same object evoked



activation in middle temporal and frontal cortices. This finding suggested that the neural processing associated with conceptual knowledge of objects was not static and localized to a specific brain region but was distributed throughout numerous cortical regions, including the sensory and motor cortices. Along similar lines, Mummery et al. (1998) showed participants the names of living things or artifacts and asked them to perform judgments of color or location. The pattern of brain activation differed depending on the attribute judgment (e.g., left anteromedial temporal cortex activation for color and left temporal-parietal junction activation for location). However, there was little difference in activation across category domains (living versus manufactured artifacts), suggesting that sensory-motor attributes accounted for a greater degree of the variance in functional activation elicited during semantic processing.

Thus far I have discussed differences between broad categories of semantic features, such as visual or motor features. However, there are many subdivisions within these sensory-motor feature domains that have been reported in the literature. For example, there is functional neuroimaging evidence that visual feature knowledge of shape (Oliver and Thompson-Schill, 2003; Ganis et al., 2004), color (Chao and Martin, 1999; Hsu et al., 2011; Grossman et al., 2013), motion (Martin et al., 2000; Kable et al., 2005), and size (Kellenbach et al., 2001) are represented in or near the distinct anatomic regions within visual association cortex involved in the perception of those specific visual features. It has also been reported that knowledge of action (Martin et al., 1995), sound (Kiefer et al., 2008; Bonner and Grossman, 2012), and smell (González et al., 2006) features depend, in part, on representations in or near the corresponding sensory-motor regions. There is even evidence that motor knowledge associated with action concepts follows the somatotopic organization of motor cortex: knowledge of face, arm, and leg

actions activates areas adjacent to and overlapping with the corresponding regions for tongue, finger, and foot movements (Hauk et al., 2004).

There are many aspects of the semantic memory system that have not been fully resolved by sensory-motor theories of semantic memory. For example, it is important to keep in mind that the neural substrates of the semantic memory system may not necessarily be the same as those underlying perception and action. Though the semantic system seems to parallel the distribution of the sensory and motor systems, these systems may still be distinct at a fine-grained neural level (Chatterjee, 2010). One specific hypothesis that addresses this issue suggests that there is an anterior shift in the location where abstract sensory-motor knowledge is stored relative to where the perception of that sensory or motor feature is processed (Martin et al., 1995; Chao and Martin, 1999; Kable et al., 2005). Additionally, the degree to which sensory-motor information is accessed may be highly influenced by the particular demands of the task. For example, concepts in semantic memory can be considered superficially or in detail, and the degree to which activations for semantic and sensory-motor processes overlap may depend on the depth of processing required for a particular semantic task (Hsu et al., 2011). Furthermore, the semantic attributes of object concepts do not consist solely of sensory-motor knowledge. There is also “world knowledge” that is more difficult to represent in a manner that is mediated by the sensory-motor system. For example, an aspect of our world knowledge for oranges is that “oranges grow in Florida”, but this information may be difficult to represent with only a set of sensory-motor features. Even within the domain of object concepts, superordinate concepts like *fruit* seem to be more abstract and rely less on sensory-motor features than basic level concepts like *apple*. Answers to some of these issues may come from a better understanding of how abstract

and cross-modal information is represented in the brain, topics which are discussed in the next two sections.

### **Abstract Knowledge**

Many of the studies discussed up to this point illustrate how the sensory and motor features of concrete concepts are represented in the brain. How does the brain represent conceptual features without direct physical referents in the world? For example, how would abstract concepts like *hope* or *truth* be stored in the brain? Much less is known about the neural basis of abstract concepts, though imaging evidence suggests that abstract and concrete concepts have partially distinct neural substrates.

An early cognitive theory, known as the dual-coding theory, suggested that abstract concepts rely primarily on a system of verbal associations, while concrete concepts rely on both verbal and sensory-feature associations (Paivio, 1971). This cognitive hypothesis would predict distinct neural correlates for these two processes, and indeed it seems to be the case that they elicit activation in partially distinct regions.

Two recent meta-analyses examined the most common loci of activation in fMRI and PET studies comparing abstract and concrete conceptual representations and found that abstract concepts tend to elicit greater activity in the left inferior frontal gyrus, left anterior middle temporal gyrus, and left anterior superior temporal gyrus (Binder et al., 2009; Wang et al., 2010). It is possible that the greater activity in the lateral temporal and inferior frontal portions of the left hemisphere, regions traditionally associated with language processes, is due to the strong reliance of abstract concepts on verbal associations, consistent with the dual-coding theory. There is additional evidence that

abstract concepts rely less on sensory-motor regions, such as visual association cortex, than concrete concepts. For example, these fMRI meta-analyses show that concrete concepts result in more activation in visual association regions of the ventral temporal lobe than abstract concepts (Binder et al., 2009; Wang et al., 2010). Additionally, a phenomenon known as “reversal of the concreteness effect” has been reported in some patients with semantic dementia. Patients with reversal of the concreteness effect exhibit a relatively worse deficit for knowledge of concrete concepts compared to abstract concepts, and it is thought that this deficit is due in part to atrophy of ventral temporal visual association regions that results in the degradation of visual feature knowledge crucial for concrete concepts (Breedin et al., 1994; Bonner et al., 2009; Hoffman et al., 2013).

Others have suggested that abstract concepts may be grounded in sensory-motor systems, similar to the way that concrete concepts are grounded (Lakoff, 1987; Barsalou, 1999). These theorists suggest that abstract concepts rely on sensory-motor simulations of experiences that intuitively capture their meaning. However, to date there are only a small number of studies in the neuroimaging literature that support this account (Barsalou, 1999; Desai et al., 2011).

It has become clear that we need a better understanding of the dimensions along which abstract concepts are organized (Crutch et al., 2013). Typically, words are categorized into abstract and concrete categories using imageability ratings. However, it may be valuable for future studies to identify the features associations that compose abstract concepts at a more fine-grained level. For example, recent work has indicated that emotional valence is an important feature dimension to consider when studying abstract concepts (Kousta et al., 2011), and it has been demonstrated that the emotional

information associated with abstract concepts may be embodied near regions of the brain that underlie the perception of emotion (Vigliocco et al., 2013).

### **Heteromodal Brain Regions And High-Level Semantic Functions**

Carl Wernicke, a well-known neurologist of the 19th century, theorized that concepts were composed of “memory traces in sensory and motor regions of cortex,” which is strikingly similar to how sensory-motor accounts would describe semantic memory a century later. But he also went on to speculate that other neural mechanisms were needed to integrate the distributed features of the memory system. As he put it, there must be some “additional mechanisms, which would explain the process of association” (Wernicke, 1900; Gage and Hickok, 2005). How is distributed semantic knowledge bound into a unified concept?

Contemporary neuroscience has begun to address the issue of high-level semantic association mostly through the consideration of heteromodal brain regions. Heteromodal brain regions are located at the convergence of multiple sensory and motor modalities and have reciprocal white matter projections to multiple, modality-specific association regions as well as other heteromodal cortices (Seltzer and Pandya, 1978; Pandya and Seltzer, 1982; Yeterian and Pandya, 1985). From a theoretical perspective, it has been proposed that heteromodal regions act as convergence zones, or hubs, where distributed features are integrated into more abstract combinations of knowledge. For example, an early proposal for the role of a convergence zone was a region where information about shape and motion converge in the conceptual representation of a

particular type of animal, or where information about shape and action converge in the conceptual representation of a particular type of tool (Damasio, 1989).

Anatomically, heteromodal brain regions display characteristics that reflect a specialization for high-level multimodal processing: they tend to have larger and more complex dendritic fields (Elston et al., 2001; Jacobs et al., 2001), lower neuron density (Collins et al., 2010), and lower myelin content (Glasser and Van Essen, 2011) when compared to primary sensory or motor cortices. Heteromodal regions are thus well situated to perform an integrative function in higher-level conceptual processing. Indeed, heteromodal brain regions are also among the most commonly activated neuroanatomic regions in functional neuroimaging investigations of semantic memory (Vigneau et al., 2006; Binder et al., 2009). These regions include lateral temporal, inferior parietal, and prefrontal cortices (Seltzer and Pandya, 1978; Yeterian and Pandya, 1985) and they are thought to support higher-level conceptual representations, including the binding of conceptual features and the selection of semantic information (Thompson-Schill et al., 1997; Binder and Desai, 2011). However, there is still much debate over which of these heteromodal regions are critical for representations in semantic memory, and exactly what kind of semantic information is represented in each heteromodal region.

One well-known heteromodal account of semantic memory is the hub-and-spoke model. This account hypothesizes that the anterior temporal lobe (ATL) is the critical locus for heteromodal semantic representations, functioning as a hub that binds together distributed semantic feature knowledge (the spokes) to create a unified concept (Patterson et al., 2007). The key motivation for this account has come from the investigation of patients with semantic dementia, which results from neurodegenerative disease affecting regions of the anterior and inferior temporal lobes. Patients with

semantic dementia have pronounced semantic memory impairments with a relative sparing of most other cognitive domains (Mummery et al., 2000; Hodges and Patterson, 2007; Bonner et al., 2010; Grossman, 2010). The deficit in semantic dementia is often characterized as amodal in nature because it is claimed that all categories of semantic information are equally affected (Patterson et al., 2007). This is consistent with the hypothesis that the ATL is an amodal semantic hub that contributes to all categories of semantic knowledge. However, some patients with semantic dementia seem to have a deficit that disproportionately affects concrete concepts, discussed before as “reversal of the concreteness effect” (Bonner et al., 2009; Macoir, 2009; Hoffman et al., 2013; Bonner et al., 2016). Furthermore, it is unclear whether the semantic representations in the ATL reflect modality-specific or heteromodal processes (Visser et al., 2010; Libon et al., 2013), and exactly which particular portions of the anterior temporal lobe are critical for this heteromodal function (Binney et al., 2012; Bonner and Price, 2013; Hoffman et al., 2015). What researchers label as the ‘ATL’ is, in reality, quite a heterogeneous group of anatomic regions. It is common for any finding in the anterior 1/3 of the temporal lobe (whether lateral, medial, dorsal or ventral) to be labeled as the ‘ATL’ (and therefore easier to interpret the findings as “amodal”), when in fact the differential contribution of subregions within the ATL may be relevant (Binney et al., 2012; Hoffman et al., 2015).

Others neuroanatomic models of semantic memory have suggested that semantic representations rely on *numerous* heteromodal association regions, emphasizing the importance of the inferior parietal lobes, lateral middle temporal gyrus, and parahippocampal cortex in semantic representation (Binder and Desai, 2011; Bonner et al., 2013; Fernandino et al., 2015; Bonner et al., 2016). The angular gyrus, a region of the inferior parietal lobe, is argued to play a particularly important role in

semantic representation by integrating the sensory and motor features of concepts into higher-level representations during thought and language, similar to how the ATL is viewed in the hub-and-spoke model (Binder and Desai, 2011; Bonner et al., 2013; Fernandino et al., 2015). This cortical region has undergone rapid evolutionary expansion in humans relative to monkeys (Orban et al., 2004; Van Essen and Dierker, 2007; Sherwood et al., 2008; Hill et al., 2010). Furthermore, during the development of the human brain this region undergoes a disproportionate expansion relative to other cortical regions between birth and adulthood (Hill et al., 2010). It is one of the most commonly activated regions in studies of lexical-semantic memory (Binder et al., 2009). However, patients with focal lesions affecting only the angular gyrus bilaterally are rare, and thus findings from the patient literature have yet to provide clear converging evidence for this function. Nonetheless, it does appear to be the case that lesions affecting the inferior parietal lobe, where the angular gyrus is located, often result in some degree of lexical-semantic impairment in patients (Benson, 1979; Damasio, 1981; Kertesz et al., 1982; Cipolotti et al., 1991; Rapcsak and Rubens, 1994; Grossman et al., 1997; Ardila et al., 2000; Grossman et al., 2003; Dronkers et al., 2004).

Other heteromodal brain regions implicated in semantic memory tasks are the ventral and dorsal prefrontal cortices (Binder et al., 2009). Regions of the prefrontal cortex are often proposed to function as domain-general processing regions that act on semantic concepts as well as other mnemonic and perceptual representations (Thompson-Schill et al., 1997; Jefferies et al., 2007). For example, prefrontal cortex is thought to support a number of high-level executive processes in semantic memory, such as retrieving specific information from memory (Wagner et al., 2001) and selecting the appropriate representation from a number of competing alternatives (Thompson-



Schill et al., 1997; Grossman et al., 2013). These investigators argue that in contrast to posterior heteromodal regions where the features of object concepts are integrated into a unified representation, prefrontal regions mediate executive functions, including logical and rule-based processes, in semantic memory. For example, there are instances in which a concept is determined by a set of abstract criteria, such as the concept “uncle,” which refers to individuals who fulfill the criterion “the brother of a parent.” It is argued that prefrontal executive mechanisms support such rule-based processes in both the acquisition and representation of concepts (Grossman et al., 2002, Grossman et al., 2007, Koenig et al., 2005, Peelle et al., 2009). Although more work is needed to further specify the many functions of prefrontal cortex in semantic memory, this region appears to be critical to the organization, retrieval, and use of semantic representations.

### **Summary Of Neuroanatomic Theories Of Semantic Memory**

Future work will benefit from understanding the degree to which semantic memory relies on an abstraction from sensory and motor experiences and the precise neural mechanisms for how this process takes place. Heteromodal regions may play a critical role in abstraction and the flexibility in the semantic system, but there is still much work to be done to fully understand how each of these heteromodal regions contribute to higher-level semantic functions. At the end of this chapter and in the Discussion chapter of this thesis, we discuss potential roles for hubs in the representation of integrated semantic knowledge.

## COGNITIVE PERSPECTIVES OF COMBINATORIAL SEMANTICS

The majority of research on the neuroanatomy and neuropsychology of semantic memory until the beginning of the 21<sup>st</sup> century focused on examining the neural representation of semantic categories of words or pictures. This work led to compelling and consistent findings at both broad levels of categorization (e.g., animate versus inanimate; living versus non-living), as well as at more specific levels of categorical distinctions (e.g., insects versus mammals). The representation of semantic categories of concepts is undoubtedly an important aspect of the neural basis of semantic memory. However, in our everyday experience we don't limit our use of concepts to categories. Indeed, concepts are not static, unitary representations, but highly interconnected entities.

On an everyday basis, we use concepts in a flexible and dynamic manner. We integrate the meaning of concepts to create more complex representations—a process referred to as conceptual combination. For example, we can represent the concepts “brown” and “dog” individually, but we can also combine their meaning to form the combination “brown dog.” The ability to perform the process of conceptual combination is essential to human cognition, and it underlies the creative nature of human thought—given the almost limitless number of combinations that can be formed (Murphy, 2002; Fodor, 2008; Hagoort et al., 2009). Even when considering only two-word combinations, there are many linguistic structures through which to formulate conceptual combinations. Common examples include adjective-noun (e.g., brown dog) and noun-noun combinations (e.g., lake house), but extend to preposition-noun combinations (e.g., under you), gerund-noun combinations (e.g., walking dogs), and many more.

Understanding how conceptual information is integrated into more complex representations of meaning is essential if we want to understand the functions of semantic memory system more broadly. Furthermore, the study of this topic may also shed light on how we view the representations and uses of semantic categories in more complex and naturalistic contexts.

The cognitive process of conceptual combination has been debated in psychology, linguistics, and philosophy for hundreds of years (Hume, 1739/1978; Fodor, 1975; Siegel, 1980; Murphy and Medin, 1985; Smith et al., 1988; Frawley, 1992; Ferris, 1993; Wisniewski, 1996, 1997; Murphy, 2002). Although there are many cognitive models for conceptual combination, there is no disagreement that this process involves integrating semantic features from across the constituents in the combination. For example, for the combination “brown dog”, some of the semantic features for “brown” and some of the semantic features for “dog” are integrated to form the meaning of a “brown dog”. This is an example of a simple adjective-noun combination, where the modifier “brown” alters the color feature of the concept “dog” such that the color attribute is increased in strength and specified to brown (Smith et al., 1988).

There are, of course, examples of adjective-noun combinations that are more challenging to interpret when using simple feature-weighted models like in the above interpretation. Fodor and Lepore (1996) argued that these kinds of models are too simplistic because they do not address challenging examples where the combination does not utilize the most typical feature dimensions of the constituent concepts (i.e. the prototypical features of the constituents). They consider the example of “pet fish” to illustrate the complexity of this process. In this example, they argue that the combination cannot be interpreted using the most prototypical features of the individual constituents

“pet” or “fish”. This conceptual combination does not easily fit into models that reweight features because it involves the emergence of features that are not common to either of the constituents, and therefore requires more than a simple reweighting of features for its interpretation. In fact, this would apply to any example where the combination has emergent features (Springer and Murphy, 1992). Indeed, it is not uncommon for adjective-noun and noun-noun combinations to elicit these kinds of emergent features (e.g., the combination “boiled celery” has the emergent property “soft”; “beach towel” has the emergent properties “brightly colored” and “protect from sand”; “fire truck” has the emergent property of “functions to put out fire”). These examples are also used to argue that conceptual combinations cannot be created using models that rely on a simple sum of the parts (i.e., a linear summation of the concept “boiled” and the concept “celery” does not give you “boiled celery”).

Another example of the semantic complexity of modifier-noun conceptual combinations are examples that involve interactions between the semantic domain and the syntax of the combination, leading to multiple potential interpretations of the same combination. For example, the combination “beautiful dancer” could be interpreted through the relation between the adjective and the noun (i.e., modifying the dancer’s ability to perform beautifully as a dancer), or it could be interpreted as the adjective modifying the noun independent of the functional role of the noun (i.e., “beautiful” modifying the visual appearance of the dancer, independent of her role as a dancer).

Modifiers that have multiple meanings in different contexts (i.e., polysemous modifiers) add another level of complexity to this problem. For example, in the combination “hard rock” and “hard day”, the modifiers are emphasizing very different semantic features of the nouns. In the case of “hard rock”, the modifier “hard” is referring

to the state of the material of a rock (i.e., solid and rigid), whereas, in the case of “hard day”, the modifier “hard” is referring to the abstract features of one’s challenging experiences over a day. In these cases, there are multiple semantic feature associations for the meaning of “hard”, and depending on the semantic domain of the noun (and other aspects of the semantic context) we have learned to flexibly focus on specific features during modification. These kinds of combinations occur most often with modifiers that can be applied in an abstract manner since abstract words often have multiple interpretations and more flexible meaning.

There is clearly a wide range of complex issues that one needs to consider when addressing the topic of conceptual combination. In order to begin understanding the neural regions that contribute to this cognitive process, I restricted my experiments to the simplest kinds of conceptual combinations. Thus, I intentionally selected adjective-noun combinations that reflected property-based modifications and produced consistent and non-ambiguous interpretations across participants (e.g., red leaf, loud car). I avoided selecting stimuli that could potentially lead to multiple interpretations (as in the “beautiful dancer” example above) or that had many emergent features (e.g., fire stairs). I also avoided using modifiers that selected abstract features of the noun (e.g., hard day) and selected adjectives that were less likely to be interpreted in a metaphoric manner. I aimed to select simple property-based modifications that referenced familiar sensory-motor properties for this initial set of conceptual combination studies in order to establish a straightforward “neural signature” of conceptual combination before delving into the many possible intricacies of this process.

## NEURAL PERSPECTIVES OF COMBINATORIAL SEMANTICS

By 2010 there had been little work on the neural basis of conceptual combination. The majority of brain-based studies examining the neuroanatomy of semantic memory had done so by presenting single-word stimuli or single-object stimuli. This is evidenced by the fact that the majority of the 120 functional neuroimaging studies that went into the 2009 meta-analysis of lexical-semantics by Binder and colleagues were studies of single-word meaning. A few of the studies in this meta-analysis included experiments with sentence stimuli but without a particular manipulation of semantic integration within the sentences. Thus the results from this aggregation of studies indicate common brain regions implicated in lexical-semantic memory, but they do not elucidate the specific regions that may be critical for the process of integrating semantic meaning during comprehension. Until early 2011, when I started to design the experiments for my thesis, there were few neuroimaging investigations specifically probing the neural correlates of conceptual combination. Of the studies that had been conducted, the majority of these studies had focused on examining the resolution of ambiguity during language processing (which we discuss below in this chapter), but almost no studies had examined simple and unambiguous conceptual combinations. More recent work has begun to examine such simple conceptual combinations, and I discuss these more recent publications in the Discussion chapter as they relate to the findings from my thesis (Chapter 5). Here I will review the studies that were published before 2011 that provided motivation for possible candidate regions for the combinatorial representations examined in my studies.

Prior functional and structural neuroimaging studies provide clues for brain regions that may be particularly important when considering the neural basis for this process. First, brain regions that support this dynamic process should be highly interconnected to many other brain regions—in other words, they should be heteromodal brain regions that can perform integration of stored knowledge across multiple feature modalities. Therefore they should possess white matter connections to many of the other brain regions involved in the lexical-semantic memory network as well as other high-level association areas near sensory-motor brain regions. Second, they should have a profile of functional connectivity that is consistent with this structural connectivity, thus demonstrating that they are highly functionally interactive. Third, they should be regions that are consistently observed across a wide variety of semantic memory tasks (since this fundamental process would be necessary for many types of semantic tasks).

In considering regions that may support the retrieval of stored (and familiar associations), one potential region that fits all the above criteria is the angular gyrus. It is a heteromodal association area that is structurally connected to many other brain regions, including a large proportion of long-range connections (Caspers et al., 2006; Caspers et al., 2008; Caspers et al., 2011). Additionally, it has also been functionally characterized as a cortical hub, exhibiting a high degree of functional correlations with a widespread network of other brain regions (Buckner et al., 2009).

The angular gyrus was described very early on in the history of neuropsychology research as a region important for the memory of word meaning and for reading. Joseph Dejerine, a French neurologist, described this region as a “word memory” region as early as 1891, based on lesions to the angular and supramarginal gyri (Dejerine, 1891). This account was then popularized by Norman Geschwind in 1965, where he described the

angular gyrus as a visual word-memory *center*, which was responsible for “carrying on visual-auditory cross-modal associations in both directions, and indeed for storing the memory of the ‘rules of translation’ from written to spoken language” (Geschwind, 1965).

However, later neuropsychology work associated lesions to this region with a constellation of symptoms. There were four symptoms particularly associated with angular gyrus lesions: dysgraphia, dyscalculia, finger agnosia, and left-right disorientation. The set of these symptoms were referred to as “Gerstmann syndrome” (when anomia is added, this is referred to as “angular gyrus syndrome”). However many of the lesions from these reports were subcortical angular gyrus lesions that penetrated large portions of white matter tracts that lay beneath the gray matter (Mayer et al., 1999; Carota et al., 2004), which may give rise to the heterogeneous symptoms of this syndrome. More recently, it has been argued that this syndrome should include the additional symptom of semantic aphasia (Ardila et al., 2000; Ardila, 2014).

The consideration of converging evidence from other primates has been challenging because it has been difficult to specify the homologous brain region in non-human primates. In fact, many neuroanatomists have observed that there is no clear homologue to this region because the inferior parietal lobe has undergone such a large degree of cortical expansion over evolution (Crosby et al., 1962; Geschwind, 1965; Zilles and Palomero-Gallagher, 2001). This region has tentatively been proposed as homologous to area PG in macaques (McCulloch, 1944; Petrides and Pandya, 2009). However, because of the debate over the extent to which this region could be ascribed to a homologous region in macaques (and considering the complexities of the cognitive processes that have been ascribed to this region) most of the early work on the angular gyrus was limited to neuropsychology research in humans.



With the advent of advanced functional neuroimaging techniques, there have been many recent studies examining brain regions that support the processing of lexical-semantic stimuli. These findings build on the findings from the early neuropsychology work. Indeed, the 2009 meta-analysis from Binder and colleagues showed that the left angular gyrus was the most commonly activated region across the 120 functional neuroimaging studies of lexical-semantic stimuli that they examined. Furthermore, it has been specifically implicated in the processing of sentences compared to word lists (Friederici et al., 2000; Vandenberghe et al., 2002; Humphries et al., 2006).

Regions within the ATL are also strong candidate regions for supporting conceptual combination. The hub within the hub-and-spoke model is proposed to integrate distinct conceptual features into coherent and unified concepts. There has been little discussion about how this cognitive process might apply when integrating features from across many different concepts during a process like conceptual combination, but it would not be an unlikely extension of this model. However, atrophy to the anterior temporal lobe correlates more strongly with impairments on single word stimuli than on sentence stimuli (Mesulam et al., 2015), which would be the opposite of what one would expect for a region that is responsible for building higher-level meaning. Nevertheless, the anterior temporal lobe is clearly a very important region for semantic memory, and a more detailed discussion of the views on ATL subregions in light of the findings from this thesis is provided in the discussion section.

One region that has received considerable attention in discussions of integration during lexical-semantic processing is the inferior frontal gyrus (IFG). This region has been shown to be activated in tasks requiring selection and retrieval of semantic knowledge (Thompson-Schill et al., 1997; Wagner et al., 2001). In particular, this region

has been shown to be involved in integrative processes that require resolving ambiguous word sequences (Hagoort, 2005; Rodd et al., 2005; Lau et al., 2008; Rodd et al., 2012), often referred to as the semantic unification theory (Hagoort, 2005). It may be that when a semantically unexpected word occurs within a given context, the IFG helps to search for novel associations that can be made in order to resolve the ambiguity and achieve comprehension (Hagoort, 2005; Lau et al., 2008). In fact, the semantic-unification theory proposes that the same mechanisms for unification are engaged even when the meaning of an ambiguous phrase or sentence is never resolved (Hagoort, 2005; Zhu et al., 2012). This means that when considering both effort and outcome, semantic unification is more associated with the processing-effort as opposed to the semantic outcome. This is an important aspect of conceptual combination to consider, but it is a different framework than how I have aimed to examine conceptual combination in the series of experiments for my thesis. Specifically, I set out to identify regions of the brain that track our ability to successfully build meaning during comprehension. In other words, these are regions that encode the semantic outcome of a combination.

## OVERVIEW OF DISSERTATION STUDIES

In this thesis, I present a series of experiments that address the following neurobiological question: What brain regions are critical for representing the meaning of simple conceptual combinations? I approach this problem using a variety of techniques that allow me to characterize the two basic properties we would expect for regions that encode combinatorial semantic representations:

- 1) In the healthy brain, these regions should exhibit a functional profile that tracks the meaning of combined semantic representations.
- 2) When these regions are perturbed, either functionally or structurally, subjects should exhibit altered behavioral recognition of conceptual combinations, while exhibiting relatively intact performance in other cognitive domains, like lower-level sensory processing.

As the first approach to examining the neural correlates of this process, I created an fMRI study to run in healthy adults (Study 1). The stimuli for Study 1 were composed of two-word combinations, where the norming data exhibited a clear divide between word pairs that readily combined to form meaningful combinations (e.g., loud car or red leaf), and those that did not readily form meaningful combinations (these were minimally meaningful two-word combinations, such as “moss pony”; I refer to these as “non-meaningful” combinations for simplicity). The design of this study aimed to test for a neural signature of conceptual combination. The logic for this design was that neural regions that are important for representing high-level semantic associations of concepts should show greater activity for meaningful combinations compared to non-meaningful

combinations (in the same way that one contrasts faces to houses in order to search for a region that is especially important for face processing). This basic contrast revealed strong effects in the left angular gyrus. We then performed planned analyses that examined individual word pairs to test for graded effects of conceptual combination in the angular gyrus, using only the word pairs that were judged to form meaningful combinations.

Studies 2 and 3 aimed to examine causal evidence that the left angular gyrus was necessary for this process. In Study 2, I examined patients with neurodegenerative disease affecting a widespread network of brain regions that included the left angular gyrus. We examined patient performance on the same stimuli used in Study 1, as well as performance on a controlled set of single words. Using a performance difference score between these two tasks, we tested for brain regions that showed a significant correlation between gray matter atrophy and a relative impairment on combinatorial processing (i.e., two-word performance compared to single-word performance).

In Study 3, I examined the effects from a form of high-definition transcranial direct current stimulation to the left angular gyrus in healthy adults. Using a much larger set of two-word stimuli, we examined reaction time changes to the processing of meaningful two-word combinations compared to non-meaningful two-word combinations. We found consistent effects across subjects that modulated the processing of meaningful combinations relative to non-meaningful combinations. As in the fMRI analysis in Study 1, we also found that this stimulation effect was graded across the individual word pairs within the meaningful word-pair category.

Across a series of three studies, I found consistent evidence that the left angular gyrus was functionally and causally involved in the process of lexical-semantic

integration. These results are consistent with the known involvement of the angular gyrus in lexical-semantic processing up until now, but extend these findings to provide evidence of a specific integrative mechanism in lexical semantics. These findings also provide the first causal evidence that the angular gyrus is necessary for combinatorial lexical-semantic processes. We provide a detailed discussion of these findings in light of other research, and possibilities for how these findings could be examined further using multivoxel analyses in Chapter 5.

The first three studies of my thesis examined combinatorial representations in language. In the last experiment, I examined a different aspect of conceptual combination: the semantic representation of visual-feature combinations in the perception of specific objects. Specifically, we examined representations that reflect the statistical regularity of color and shape combinations for objects in the natural environment. These representations reflect information that is specifically tied to the combination of color and shape features and cannot be obtained from consideration of either feature alone. This research aimed to address the following question about semantic codes for visual objects: What brain regions encode representations of the feature combinations that define an object's meaning? Using a multivariate approach for analyzing representational codes in fMRI data, we identified strong effects in perirhinal cortex, a subregion of the anterior temporal lobe that has previously been linked with research on both object perception and high-level semantics. These results point to a high-level hub at the apex of the visual-processing stream that represents semantic-feature combinations for visual objects.

Altogether this work identifies two key regions implicated in the representation of combinatorial information in semantic memory. We identified consistent findings that the

left angular gyrus is involved in representing a neural signature of the combined meaning of two words during language processing. In the final study, we identified a region of the ventral anterior temporal lobe that encodes fine-grained knowledge of the feature combinations that define the meaning of individual visual objects.

## CHAPTER 2

### **Converging evidence for the neuroanatomic basis for combinatorial semantics**

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#### **ABSTRACT**

Human thought and language rely on the brain's ability to combine conceptual information. This fundamental process supports the construction of complex concepts from basic constituents. For example, both “jacket” and “plaid” can be represented as individual concepts, but they can also be integrated to form the more complex representation “plaid jacket”. Although this process is central to the expression and comprehension of language, little is known about its neural basis. Here we present evidence for a neuroanatomic model of conceptual combination from three experiments. We predicted that the highly integrative region of heteromodal association cortex in the angular gyrus would be critical for conceptual combination, given its anatomic connectivity and its strong association with semantic memory in functional neuroimaging studies. Consistent with this hypothesis, we found that the process of combining concepts to form meaningful representations specifically modulates neural activity in the angular gyrus of healthy adults, independent of the modality of the semantic content being integrated. We also found that individual differences in the structure of the angular gyrus in healthy adults are related to variability in behavioral performance on the conceptual combination task. Finally, in a population of patients with neurodegenerative

disease, we found that the degree of atrophy in the angular gyrus is specifically related to impaired performance on combinatorial processing. These converging anatomic findings are consistent with a critical role for the angular gyrus in conceptual combination.



## INTRODUCTION

A major goal of neuroscience is to understand the neural basis of behaviors that are fundamental to human intelligence. One such behavior is the ability to combine conceptual information in language and thought. This combinatorial process allows humans to dynamically construct an unlimited number of complex concepts from a finite set of constituents. For example, we can take the basic concepts “leaf” and “wet” and combine them to create the representation of a “wet leaf”. The cognitive processes supporting conceptual combination have long been investigated in psychology and philosophy, but little is known about their neural basis (Hume, 1739; Fodor and LePore, 2002; Murphy, 2002).

Most neuroanatomic theories of semantic memory have focused on the representation of individual concepts (Pulvermüller, 2005; Martin, 2007; Patterson et al., 2007; Binder et al., 2009). Much of this work has examined the role of sensory and motor association cortices in representing the features of individual concepts (e.g., the sound feature of “thunder” is thought to be represented in or near auditory association cortex (Bonner and Grossman, 2012)). Some of this work has also examined the role of high-level heteromodal association cortices, sometimes referred to as “hubs,” in representing the amodal associations of concepts (e.g., the intrinsic knowledge that “apples” are edible fruit (Patterson et al., 2007; Binder et al., 2009)). However, few studies have directly examined the neural basis for how individual concepts are combined into more complex representations.

Here we test the prediction that conceptual combination relies in part on the heteromodal association cortex of the angular gyrus. Anatomically, the angular gyrus is

well situated to perform this type of integration. It has widespread white matter connectivity with sensory and motor association cortices as well as with classic language regions, such as the inferior frontal and superior temporal cortices (Seltzer and Pandya, 1978; Pandya and Seltzer, 1982; Yeterian and Pandya, 1985; Mesulam and Mesulam, 2000; Bonner et al., 2013). The cytoarchitectonic properties of the angular gyrus also reflect a specialization for high-level multimodal processing: Relative to unimodal cortices, heteromodal brain regions like the angular gyrus have larger and more complex dendritic fields, indicating diverse and highly integrative computations (Elston et al., 2001; Jacobs et al., 2001). Furthermore, the angular gyrus is one of the most commonly activated regions in functional neuroimaging studies of semantic memory (Binder et al., 2009).

Here we demonstrate that the angular gyrus supports the integration of individual concepts into coherent semantic combinations. In three experiments we find that: 1) neural activity in the angular gyrus increases during conceptual combination; 2) anatomic variability in the angular gyrus in healthy adults predicts individual differences in the processing of combined concepts; and 3) atrophy of the angular gyrus in patients with neurodegenerative disease results in impaired conceptual combination. These findings build on previous work that more broadly implicates the angular gyrus in semantic representation, and indicate a specific, high-level function for semantic integration.

## MATERIALS AND METHODS

### *Healthy adult experiments*

#### *Participants*

Twenty-two healthy adults from the University of Pennsylvania community participated in the study (10 female; mean age = 25.3 years; range = 19-36). All were right-handed native English speakers with no history of neurological difficulty, as determined by a pre-experiment screening. We obtained informed consent from all participants according to a protocol approved by the University of Pennsylvania Institutional Review Board.

#### *Experimental design and task stimuli*

Our experimental design aimed to isolate the neural activity associated with the basic process of combining conceptual information in a semantically meaningful manner. To do this, we examined the processing of adjective-noun combinations. We created sets of word pairs that systematically varied in how readily the words could be integrated into a combined concept (as determined in a series of norming studies, discussed below). The word pairs could be divided into pairs that readily combined to form meaningful conceptual combinations (e.g., plaid jacket) and pairs that did not readily combine to form meaningful combinations (e.g., moss pony). We also manipulated the type of sensory-motor information associated with the combination so that there were four different sensory-motor semantic categories of meaningful combinations: auditory, motion, tactile, and visual. For example, the first word modified the second word in a manner that was strongly auditory (n = 28; e.g., *loud* car), motion (n = 28; e.g., *drifting* balloon), tactile (n = 28; e.g., *gooey* candy), or visual (n = 28; e.g., *plaid* jacket). The

second word always referred to a concrete object. We refer to these four categories here as the “meaningful combinatorial word pairs.”

To develop the stimuli, we first collected association ratings from 20 young adults on 371 adjectives and 489 nouns for how strongly each word was associated with each of the four sensory-motor features on a 1-to-7 scale: sound, motion, tactile, and visual association ratings. From these, we then created 4 categories of word pairs ( $n = 28$  per category) based on the sensory-association ratings of the modifier (i.e., the first word). These word pairs were balanced on summed values for letter length, word frequency (Brysbaert and New, 2009), co-occurrence frequency (see below), orthographic neighborhood density (Medler and Binder, 2005) and syllable number (all pairwise t-test comparisons  $p > 0.2$ ). Across all conditions, nouns were highly imageable and did not differ on any of the four sensory-motor feature associations (all pairwise t-test comparisons  $p > 0.2$ ). We also collected sensory-motor feature association ratings on a 1 to 7 scale for each word pair (i.e., at the phrase-level) to confirm that the phrase-level associations were similar to those obtained in the single-word norming data. Sound feature associations were highest for the sound word pairs (sound association ratings: sounds word pairs = 6.5 (0.4); motion word pairs = 2.5 (0.8); tactile word pairs = 1.5 (0.5); visual word pairs = 1.3 (0.2); all t-tests  $p < 0.001$  in comparisons of sound words with other groups). Motion feature associations were highest for the motion word pairs (motion association ratings: motion word pairs = 6.2 (0.6); sounds word pairs = 3.1 (0.6); tactile word pairs = 1.5 (0.3); visual word pairs = 1.4 (0.4); all t-tests  $p < 0.001$  in comparisons of motion words with other groups). Tactile feature associations were highest for the tactile word pairs (tactile association ratings: tactile word pairs = 5.8 (0.6); sounds word pairs = 1.6 (0.6); motion word pairs = 1.5 (0.2); visual word pairs = 1.6

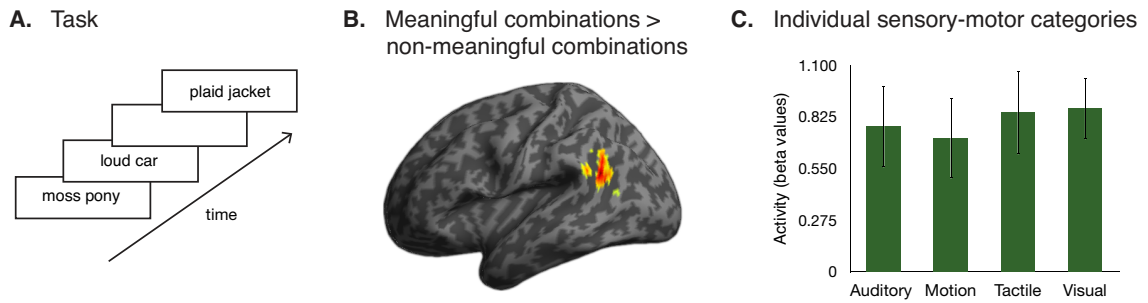
(0.6); all t-tests  $p < 0.001$  in comparisons of tactile words with other groups,). Visual feature associations were highest for the visual word pairs (visual association ratings: visual word pairs = 6.7 (0.3); sounds word pairs = 4.2 (0.6); motion word pairs = 5.4 (0.4); tactile word pairs = 4.4 (0.8); all t-tests  $p < 0.001$  in comparisons of visual words with other groups).

We next constructed a baseline of two real words that were judged to combine less meaningfully, which we refer to as the “non-meaningful” baseline (e.g., moss pony;  $n = 28$ ). These word pairs did not differ statistically from the meaningful combinatorial word pairs on any of the sum sensory-motor feature associations (auditory, motion, tactile, or visual). They also did not differ statistically from any of the meaningful combinatorial word pair categories on summed values for word frequency (Brysbaert and New, 2009), letter length, concreteness, orthographic neighborhood density, or number of syllables (all pairwise t-tests comparisons  $p > 0.1$ ). We also included two low-level baseline conditions containing a pronounceable pseudoword paired with a concrete noun (e.g., sloke road;  $n = 28$ ) and a pronounceable pseudoword paired with another pronounceable pseudoword (e.g., micked yark;  $n = 28$ ). These last two were included as additional low-level baselines, but are not used in the analyses presented here.

Next, we collected plausibility ratings on a 1-to-7 scale for all of the word pairs in order to ensure that subjects considered: (1) that meaningful combinatorial word pairs formed highly plausible combinations and (2) that non-meaningful combinatorial word pairs formed highly implausible combinations ( $n = 24$  healthy adults; meaningful combinatorial word pairs average rating = 6.22; non-combinatorial word pairs average rating = 1.75;  $t(138) = 27.5$ ,  $p < 0.001$ ).

The norming study also revealed that subjects treated the plausibility of

conceptual combinations as a continuous factor rather than a dichotomous one (i.e., within the category of “meaningful” combinations, some concepts formed stronger combinations than others). To explore this issue further, we obtained an objective, quantitative measure of how frequently our stimulus items co-occurred in written text, allowing us to test more fine-grained predictions about the neural basis for conceptual combination. We hypothesized that more frequent word combinations would be judged as more plausible. A large corpus was needed to capture the variability of co-occurrence frequencies across word pairs. To do this we determined the number of times the two words occurred together in a particular order within all web pages ending in “.com” that are indexed on Google (i.e., assessing unidirectional co-occurrence, which is how frequently the words “plaid jacket” occur together in sequence but not in the reverse sequence “jacket plaid”). Specifically, we identified the number of search hits for a particular word combination and took the log of this value to generate the log co-occurrence frequency. We refer to this measure as the “combinatorial strength” of the word pairs. This measure strongly correlated with the behavioral plausibility ratings of the word pairs that we collected separately in 24 healthy adults (Spearman’s  $\rho = 0.55$ ;  $p < 0.001$ ). There were no differences in the log co-occurrence frequencies between the 4 sensory-motor combinatorial categories. The distribution of log co-occurrence frequencies for all meaningful combinations is illustrated in Figure 3A.



**Figure 2.** Activity in the angular gyrus was modulated by meaningful combinations, independent of the category of semantic information forming the combination. A. Subjects viewed pairs of real words whose combinations were considered to be meaningful (e.g., plaid jacket) or non-meaningful (e.g., moss pony) based on the results of a norming study. B. fMRI activation in healthy adults for the meaningful combinatorial word pairs relative to the non-meaningful combinatorial word pairs ( $p < 0.001$  voxelwise, cluster-level  $p < 0.05$  whole-brain corrected for family wise error; this was a cluster of  $4584\mu\text{l}$  with a peak at  $[-52 -56 22]$ ). C. There were no differences in activation between the four sensorimotor semantic categories of meaningful combinations within the left angular gyrus activation cluster shown in B (error bars represent  $\pm 1$  SEM).

### *Procedure*

The fMRI experiment used an event-related design, illustrated schematically in Figure 2. On each trial, a fixation cross was presented for 500 ms followed by the display of the word pair for 2500 ms. Before the experiment, participants received a practice session to ensure that they understood the task. Participants were instructed to press one button if the displayed word pair formed a meaningful combination and another button if it did not (buttons were randomized equally across participants). Stimuli were presented in a random sequence order across 3 different scanning blocks with a brief pause between blocks. One quarter of all events were null events (3 seconds in duration).

### *Image acquisition and analysis in healthy adults*

Subjects were scanned on a Siemens 3.0T Trio scanner. We acquired T1-weighted structural images using an MPRAGE protocol (TR = 1620 ms, TE = 3.9 ms, flip angle = 15°, 1 mm slice thickness, 192 × 256 matrix, resolution = 0.9766 × 0.9766 × 1 mm), followed by blood oxygenation level-dependent (BOLD) fMRI images (TR = 3 sec, TE<sub>eff</sub> = 30 ms, flip angle = 90°, 64 × 64 matrix, 3 mm isotropic voxels, and fat saturation).

We processed the T1-weighted structural images with PipeDream (<https://sourceforge.net/projects/neuropipedream/>) and Advanced Normalization Tools (ANTS; <http://www.picsl.upenn.edu/ANTS/>) (Avants et al., 2008). The images were inhomogeneity-corrected using the N4ITK algorithm (Tustison et al., 2010), warped to a local template space using symmetric diffeomorphic normalization in ANTS, segmented into tissue probability maps using template-based priors, and then registered to MNI-template space. We examined voxel-based cortical thickness using a registration-based cortical thickness measure (Das et al., 2009; Tustison et al., 2014). This method uses a continuous one-to-one correspondence between the gray matter–white matter interface and the gray matter–cerebrospinal fluid interface given by a diffeomorphic mapping in the image space, and defines thickness in terms of a distance measure between the interfaces of this sheet-like structure. The preprocessed images were further analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK), including smoothing with an 8-mm full-width at half maximum (FWHM) Gaussian kernel.

We processed and analyzed the fMRI images using SPM8. Each subject was modeled individually. All functional images were realigned to the first image, coregistered with the structural image, and normalized to standard Montreal Neurological Institute (MNI) space using unified segmentation with resampling of images



into isotropic 2 mm voxels. We inspected movement parameters generated during image realignment. Three participants who moved more than 2 mm during the functional sessions were excluded from the functional analyses. No other subjects moved more than 1 mm during the entire scan. We spatially smoothed the images using an 8 mm FWHM isotropic Gaussian kernel. To remove low-frequency drifts, we applied a high-pass filter with a cutoff period of 90 s. We modeled autocorrelations with a first-order autoregressive model. For all whole-brain analyses, we used a cluster-defining threshold of  $p < 0.001$  uncorrected, and performed a cluster-level correction for family-wise error (FWE) across the whole brain at  $p < 0.05$  using random field theory (Worsley et al., 1992).

#### *Functional imaging in healthy adults: subject analysis*

In the subject-level analysis, first-level models were created for each subject individually using a general linear model of the BOLD signal with regressors for each category and with movement parameters included as covariates of no interest. In order to make inferences across participants, we entered the parameter estimates into a second-level random effects analysis, with subjects as random variables.

#### *Functional imaging in healthy adults: item-analysis*

We performed an item analysis (Bedny et al., 2007) in which each meaningful combinatorial word pair was modeled individually and then averaged across all subjects. The first-level analysis included a covariate for every single adjective-noun combinatorial item individually ( $n = 112$ ;  $n = 28$  per sensory-motor category), and a single covariate for each of the non-combinatorial conditions plus an additional covariate for each scanning session (yielding a total of 118  $\beta$ -maps). Next the  $\beta$ -maps for each covariate were averaged across all subjects in order to perform the second-level analysis. Thus, a voxel

within each  $\beta$ -map contained the averaged  $\beta$ -value for that item, derived from all subjects. To test the correlation of combinatorial strength and activity across the 112 combinatorial items, we performed a regression analysis using the combinatorial strength and the individual  $\beta$ -maps for each item, allowing us to look at the regions that positively correlated with combinatorial strength.

#### *Anatomically-defined regions of interest in the healthy adults*

Regions of interest (ROIs) for the left angular gyrus, left middle temporal pole, and right angular gyrus were created using anatomic labels (Tzourio-Mazoyer et al., 2002) defined in the WFU Pick Atlas (Maldjian et al., 2003). We ensured that signal strength in the temporal pole ROI was maximized by constraining it to voxels that had a signal of at least 80% of the global signal for each participant (Devlin et al., 2000).

### ***Patient Experiment***

#### *Participants*

To ensure that we would be able to detect possible anatomic effects across a range of cortical regions, we examined a heterogeneous group of patients with cortical atrophy affecting portions of the parietal, frontal, occipital, and temporal lobes. Twenty patients with clinically diagnosed dementia from neurodegenerative disease participated in this study (see Table 1 for details; 7 females). Patients were diagnosed according to published criteria (Albert et al., 2011; Gorno-Tempini et al., 2011; McKhann et al., 2011; Rascovsky et al., 2011) and diagnoses were confirmed in a consensus conference based on a review of a semi-structured history, a comprehensive mental status exam, and a complete neurological exam by at least two independent, trained reviewers. All

participants and their legal representatives participated in an informed consent procedure approved by the University of Pennsylvania institutional review board.

### *Experimental design*

To allow for direct comparisons with the fMRI study in healthy adults, patients performed the same combinatorial task described above, as well as a previously published single-word lexical decision task (Bonner and Grossman, 2012; Bonner et al., 2013). In the single-word lexical decision, patients viewed a single word presented on the screen and indicated by button press whether the word was a real word (e.g., pyramid) or a pronounceable pseudoword (e.g., dranby). There were no words repeated between the combinatorial and single-word tasks. The words from the combinatorial task and the single-word lexical decision task were additionally matched on average frequency ( $t(270) = 0.05$ ,  $p = 0.96$ ) and average letter length per word ( $t(270) = 1.03$ ,  $p = 0.30$ ).

### *Image acquisition and analysis in patients*

T1-weighted structural images were acquired with the same protocol described in the healthy-adult experiment above, and the images were analyzed with PipeDream, ANTS, and SPM8. Gray matter density images were obtained from tissue probability maps through segmentation with template-based priors. These were then registered to MNI-template space and smoothed with an 8 mm FWHM Gaussian kernel. We constrained all statistical analyses to gray matter using an explicit mask, defined by generating a mean gray matter probability image from all subjects and thresholding at 0.2. For the whole-brain analysis, we applied the same statistical threshold as in the above analyses

in healthy adults, using random field theory with an adjustment for non-stationarity (Hayasaka et al., 2004).

## RESULTS

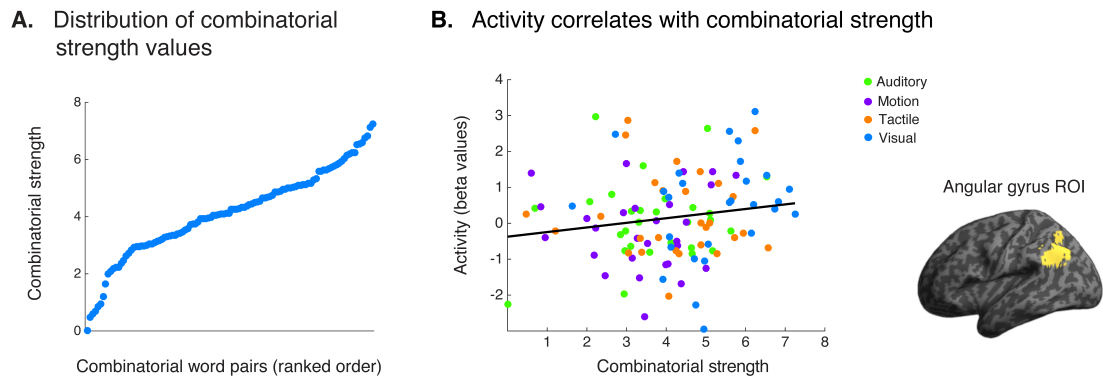
### *Behavioral results in healthy adults*

Subjects were highly accurate on the combinatorial semantic judgment task (mean accuracy = 95.5 %, SD = 3.5). There was no significant difference in accuracy between the meaningful and non-meaningful combinatorial word-pair conditions ( $t(21) = 1.3$ ,  $p = 0.22$ ). Reaction times were faster for the meaningful combinations (meaningful combinatorial mean = 1178.7 ms, SD = 215.4 ms; non-meaningful combinatorial mean = 1358.7 ms, SD = 231.6 ms;  $t(21) = 5.6$ ,  $p < 0.001$ ).

### *Functional neuroimaging in healthy adults*

To examine the neural regions that support semantic combinations, we performed a whole-brain analysis of the fMRI data. We first identified regions where there was more activity for the more meaningful compared to the less meaningful combinations. This analysis revealed a significant cluster of activity in the left angular gyrus, shown in Figure 2B. No other brain regions showed significant activation for this contrast. We next determined whether this effect reflected a multimodal combinatorial process or one that was specific to a particular sensory-motor modality of semantic information. In order to address this question, we examined whether there were differential effects across four sensory-motor categories of word pairs. As shown in Figure 2C, a repeated measures

ANOVA showed no differences between the sensory-motor word categories within the left angular gyrus ( $F(3, 54) = 0.13, p = 0.94$ ).



**Figure 3.** Activity in the angular gyrus increased as a function of the combinatorial strength of individual word pairs modeled in an item analysis. A. The distribution of combinatorial strength values (log co-occurrence frequencies) for all meaningful combinatorial word pairs, ranked from lowest to highest. B. An item analysis revealed that activity in the left angular gyrus correlated with the combinatorial strength of the word pairs. This correlation was performed using only the meaningful combinatorial pairs, and fMRI activity was extracted from an anatomically defined region of interest in the left angular gyrus (see Materials and Methods for details).

We next examined a continuous measure of conceptual combination within the more meaningful combinations and related this to a graded effect in the fMRI data by performing an item analysis. Figure 3A shows the distribution of log co-occurrence frequencies across the meaningful combinations. As noted above, this measure highly correlated with a subjective measure of combinatorial plausibility. We predicted that combinatorial strength would be related to the degree of activation in the angular gyrus. As shown in Figure 3B, we found that activity in the left angular gyrus was positively correlated with the degree of combinatorial strength across all items (Spearman's  $\rho =$

0.21,  $p < 0.05$  Bonferroni-corrected for the two ROIs tested). Within the ROI in the left anterior temporal lobe we found no correlation between neural activity and combinatorial strength (Spearman's  $\rho = 0.05$ ,  $p > 0.9$  Bonferroni-corrected). Finally, we performed a whole-brain regression analysis of these data to ensure there were no regions outside our pre-selected ROIs that showed this effect. In this whole-brain regression, the right angular gyrus was the only region in which item-level neural activity correlated with combinatorial strength (a cluster of 5624  $\mu\text{L}$  with a peak at [62 -38 38]).

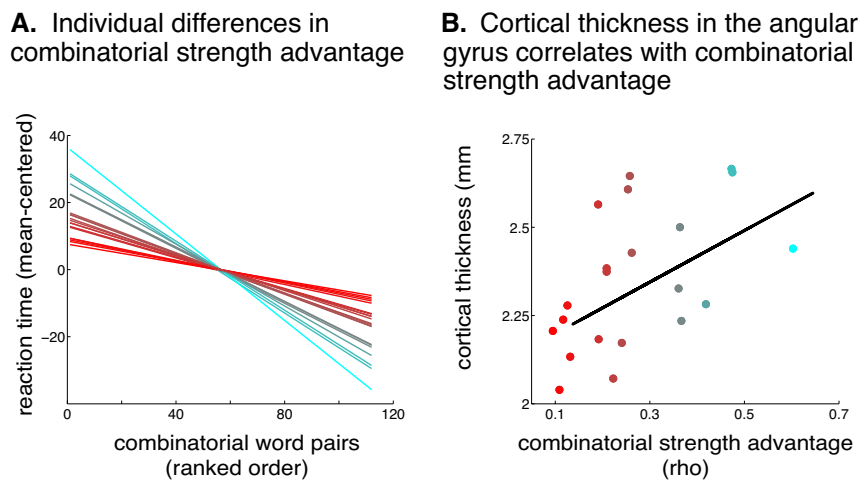
We next examined whether left and right angular gyri were performing functionally distinct combinatorial operations by directly comparing the correlations using anatomically defined right and left angular gyrus ROIs. We performed a Fisher's  $r$ -to- $z$  transformation on the correlations between neural activity and combinatorial strength within each ROI and compared these. There was no significant difference between the effects in the left and right angular gyri ( $z = 0.3$ ,  $p = 0.76$ ). Rather, the effects in the left and right angular gyri were highly correlated across word pairs (Spearman's  $\rho = 0.79$ ,  $p < 0.001$ ).

Together, these results demonstrate a relationship between neural activity in the angular gyrus and conceptual combination. These findings show that the angular gyrus is activated during the processing of meaningful combinations and that the degree of activation in the angular gyrus scales with a continuous measure of combinatorial strength.

### *Structural neuroimaging in healthy adults*

As discussed above, subjects displayed a processing advantage in their behavior for high combinatorial-strength word pairs relative to low combinatorial-strength word pairs

(i.e., faster reaction times for items with high combinatorial strength). However, there were individual differences in the extent to which subjects showed this processing advantage, shown in Figure 4A. Some subjects had a stronger processing advantage (in blue) while other subjects showed a weaker processing advantage (in red). We hypothesized that individual differences in the degree of this processing advantage would be related to individual differences in the structure of the left and right angular gyri.



**Figure 4.** In healthy adults, individual differences in performance on the combinatorial task were related to individual differences in the structure of the angular gyrus. A. This plot shows the relationship for each subject between reaction time and the combinatorial strength of the stimuli. Each line represents a regression within a single subject. As a group, subjects showed a performance advantage for high-combinatorial word pairs relative to low-combinatorial word pairs. However, subjects varied on the extent to which they exhibited this performance advantage, which is illustrated by the range of regression lines in this figure (cooler colors = stronger advantage, warmer colors = weaker advantage). B. Individual differences in the degree of this performance advantage were correlated with individual differences in the cortical thickness of the right angular gyrus (whole-brain corrected cluster from the fMRI item analysis). The combinatorial strength values used in this analysis reflect the relationship between reaction time and the combinatorial strength of the stimuli within each subject, as shown in A. They are calculated by taking the negative of the Spearman's  $\rho$  values from a correlation of reaction time and combinatorial strength. See Results for an analysis of a single outlier in cortical thickness.

We tested this hypothesis by examining cortical thickness within functionally defined regions of the left and right angular gyri. We also examined an anatomical region of interest in the left anterior temporal lobe. Indeed, we found that cortical thickness in the right angular gyrus was strongly correlated with the degree of the processing advantage for high relative to low combinatorial items (Fig. 3B; Spearman's  $\rho = 0.583$ ,  $p = 0.008$ ; all structural correlations were one-tailed and Bonferroni-corrected for three multiple comparisons), whereas cortical thickness in the left angular gyrus and the left anterior temporal lobe showed no significant relationship with the combinatorial processing advantage (left angular gyrus: Spearman's  $\rho = 0.340$ ,  $p = 0.183$ ; left anterior temporal lobe: Spearman's  $\rho = 0.355$ ,  $p = 0.158$ ). This finding demonstrates that even in healthy adults, individual variability in the structure of the right angular gyrus is related to individual variability in the processing of combined semantic information.

One subject in the structural analysis was an outlier, with a cortical thickness value in the right angular gyrus (3.2 mm) that was more 3 standard deviations away from the mean of the other subjects (mean 2.4 mm, SD = 0.26). We therefore removed this subject from the correlation analyses. We note, however, that even if this participant is left in the analysis, it does not change the significance of the correlations (e.g., right angular gyrus:  $\rho = 0.576$ ,  $p = 0.008$ ; left angular gyrus:  $\rho = 0.303$ ,  $p = 0.256$ ; left anterior temporal lobe:  $\rho = 0.354$ ,  $p = 0.159$ ).

### *Structural neuroimaging in patients*

We next addressed the critical question of whether atrophy of the angular gyrus results



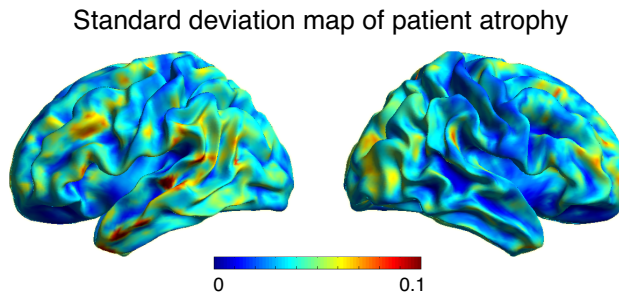
in impaired comprehension of conceptual combinations by testing a group of patients with cortical atrophy from neurodegenerative disease (see Table 1 and Figure 5). We administered the same combinatorial task performed by healthy adults in the fMRI experiment to patients. We additionally administered a separate single-word lexical decision task to assess the patients' single-word knowledge. We predicted that atrophy of the angular gyrus would result in a relatively greater impairment for combined concepts relative to impairments with single words. To test this, we calculated a difference score between performance on the combinatorial task and performance on the single-word task within each patient. This difference score provided a specific measure of the patients' relative performance on combined concepts, while controlling for general impairments with lexical access and other lower-level cognitive functions also engaged by the single-word task.

We first examined whether the degree of impaired performance on combined concepts was related to atrophy in the region of the left angular gyrus that was activated in the fMRI study of healthy adults (i.e., Fig. 1B). Indeed, we found that in patients the degree of atrophy in this region was associated with the degree of impaired performance on the combinatorial task relative to the single-word task (Fig. 5A; Spearman's  $\rho = -0.73$ ,  $p < 0.001$ , one-tailed). We next performed a whole-brain regression analysis (Table 2) which revealed that the relative deficit on the combinatorial task was strongly associated with atrophy in the left and right angular gyri, shown in Figure 6B. There was considerable overlap with the anatomic findings from the patient experiment and the fMRI experiment in healthy adults, illustrated in Figure 6C.

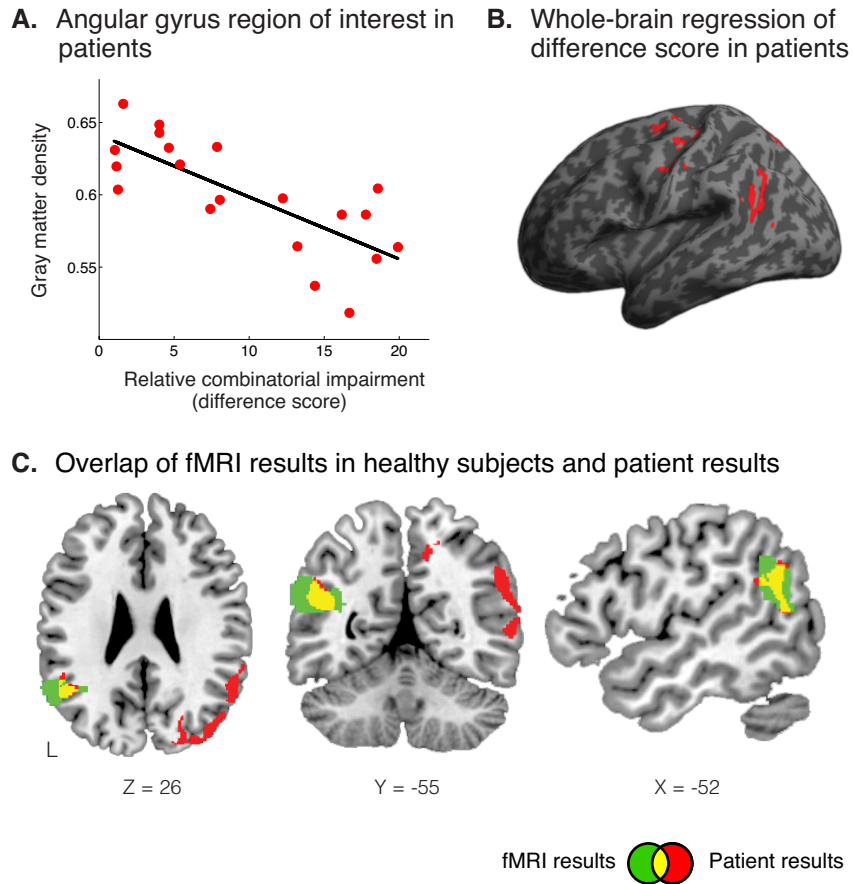
Syndrome	Single-word task (accuracy%)	Combinatorial task (accuracy %)	Difference score (%)	Gray matter density in angular gyrus	MMSE score	Age at test
PCA	97.1	77.2	19.9	0.56	25	59
lvPPA	91.8	73.2	18.6	0.6	17	64
bvFTD	93.9	75.4	18.5	0.56	23	65
bvFTD	93.2	75.4	17.8	0.59	25	61
CBS	87.7	71	16.7	0.52	17	62
svPPA	80	63.8	16.2	0.59	24	66
bvFTD	97.9	83.5	14.4	0.54	24	63
PCA	97.1	83.9	13.2	0.56	22	70
svPPA	67.1	54.9	12.2	0.6	16	64
bvFTD	96.4	88.4	8	0.6	26	77
MCI	98.9	91.1	7.9	0.63	28	63
MCI	84.6	77.2	7.4	0.59	26	55
svPPA	82.1	76.8	5.4	0.62	27	70
bvFTD	97.5	92.9	4.6	0.63	28	64
lvPPA	98.2	94.2	4	0.64	30	72
ALS	100	96	4	0.65	17	53
lvPPA	98.9	97.3	1.6	0.66	29	52
lvPPA	96.8	95.5	1.3	0.6	29	62
lvPPA	98.9	97.8	1.2	0.62	30	61
MCI	95.7	94.6	1	0.63	26	66

CBS, corticobasal syndrome; bvFTD, behavioral variant frontotemporal dementia; PCA, posterior cortical atrophy; MCI, mild cognitive impairment; lvPPA, logopenic variant of primary progressive aphasia; svPPA, semantic variant of primary progressive aphasia; difference score: single-word task accuracy — combinatorial task accuracy; MMSE, mini-mental state examination (max = 30).

**Table 1.** Demographic characteristics and behavioral performance of patients



**Figure 5.** Whole-brain map of the SD of patient atrophy. The value in each voxel represents 1 SD of gray matter density across the 20 patients, where warmer colors indicate greater variability in atrophy.



**Figure 6.** In patients with neurodegenerative disease, the degree of atrophy in the angular gyrus was related to the degree of specific impairment on combinatorial performance. **A.** Gray matter density in the left angular gyrus of patients strongly correlated with the degree of impaired performance on the combinatorial task relative to the single-word task (relative combinatorial impairment score = overall accuracy on the single-word task - overall accuracy on the combinatorial task). **B.** A whole-brain regression shows regions where gray matter atrophy was strongly related to the relative combinatorial impairment in patients. There was a strong effect in the angular gyrus. **C.** Overlap (shown in yellow) of the fMRI results from Figure 2A (shown in green) and the patient regression results (shown in red). This illustrates the considerable overlap of the experimental findings from the fMRI and patient studies.

<i>X</i>	<i>Y</i>	<i>Z</i>	Cluster size ( $\mu$ )	Z-score
30	-41	-6	3694	5.00
21	-48	-6		4.09
37	-33	-7		3.69
46	-78	21	16326	4.70
55	-37	10		4.48
38	-67	44		4.48
-42	-56	22	2301	4.64
-56	-61	14		4.14
-53	-51	24		3.37
23	-18	67	897	4.59
18	-23	71		4.06
32	-18	58		3.92
33	0	56	532	4.50
41	6	55		3.97
-19	-18	65	760	4.42
-24	-7	55		3.75
-15	-14	72		3.25
24	-73	-10	1112	4.39
11	-76	-4		3.95
-41	-16	53	2030	4.36
-30	-32	52		3.86
-43	-14	38		3.73
-22	-76	-5	1170	4.12
-21	-57	-7		3.93
31	-24	52	1689	4.05
47	-7	53		4.03
34	-15	46		3.86
58	-26	18	763	4.05
43	-28	13		3.43

Significant clusters from the whole-brain regression analysis in patients with peaks and subpeaks. Coordinates are in MNI space.

**Table 2.** MRI clusters from patient regression analysis

## DISCUSSION

An unresolved question in human cognition is how the brain integrates conceptual information into coherent representations. In this series of experiments we found converging evidence from patients and healthy adults that the angular gyrus is a critical region underlying this process. In healthy subjects, we found that activity in the angular gyrus is modulated by the integration of words into meaningful combinations.

Furthermore, we found that the processing of combined concepts in healthy adults is related to individual differences in the structure of the angular gyrus. Finally, we found that atrophy of the angular gyrus in patients with neurodegenerative disease is associated with a greater impairment on combined concepts relative to individual concepts, demonstrating a necessary role for this region in conceptual combination. These novel findings provide important new insights into the neuroanatomic basis of conceptual combination, and suggest that a key function of the angular gyrus is to support the representation of integrated semantic information.

Our results are consistent with the known anatomic and functional properties of the angular gyrus. The cytoarchitecture and white-matter connectivity of the angular gyrus are well suited to perform the heteromodal integrative functions required for a process like conceptual combination (Elston et al., 2001; Jacobs et al., 2001; Orban et al., 2004; Sherwood et al., 2008; Collins et al., 2010; Hill et al., 2010; Glasser and Van Essen, 2011). Additionally, comparative anatomic studies suggest that it has undergone a prominent evolutionary expansion in humans relative to monkeys (Orban et al., 2004; Sherwood et al., 2008; Hill et al., 2010). Functionally, it is one of the most commonly

activated regions in studies of lexical-semantic memory (Binder et al., 2009), and it has been specifically implicated in the processing of sentences compared to word lists (Friederici et al., 2000; Vandenberghe et al., 2002; Humphries et al., 2006), with an activation profile that specifically correlates with the number of sequentially coherent words in a sentence (Pallier et al., 2011). Altogether, these neurobiological properties are consistent with a fundamental role for the angular gyrus in performing integrative functions in semantic memory.

Of the few studies that have specifically examined the neural correlates of basic combinatorial processing, some have emphasized the role of the anterior temporal lobe (Baron et al., 2010; Bemis and Pykkänen, 2011, 2013) while other work has implicated the right angular gyrus (Graves et al., 2010) and left angular gyrus in this process (Bemis and Pykkänen, 2013). Here, we found strong, converging evidence from three different experiments that the left angular gyrus is critical for the process of conceptual combination. We did not find any significant results that implicated the anterior temporal lobe in our comparisons. Although fMRI is known to be susceptible to signal loss in the medial and inferior temporal regions (Devlin et al., 2000), we also did not find evidence linking the anterior temporal lobe to combinatorial processing in our structural imaging studies, which are less susceptible to signal drop-out in this region. It will be of interest in future work to determine the differential contribution of the anterior temporal lobe and the angular gyrus in integrative semantic processes.

The grammatical categories of the stimuli may also be relevant when interpreting differences across studies. For example, when reading adjective-noun pairs, one has a strong expectation that the adjective will be followed by a noun with which it should be combined. On the other hand, when reading noun-noun pairs, as used in Graves et al.

(2010), readers may not expect the first noun to act as a modifier in a semantic combination. This may result in more semantic searching or re-evaluation when processing noun-noun combinations.

Past work has been limited to the use of categorical contrasts to identify the loci of anatomic regions that contribute to combinatorial processing. Here we build on previous findings and advance a novel framework for conceptual combination by characterizing a continuous metric that is critical for understanding combinatorial processes. We found that a metric of co-occurrence frequency strongly correlates with how plausible a combination is perceived to be and that this metric is associated with a graded neural response in the fMRI data as well as individual differences in how healthy adults process combined concepts. By taking this continuous and objective measure into consideration, we were able to test more fine-grained hypotheses about the neural basis of conceptual combination. Future studies may benefit from considering differences in co-occurrence frequency between more and less meaningful combinatorial conditions.

Our patient study is the first test of whether the angular gyrus is necessary for conceptual combination. Previous neuroanatomic studies of conceptual combination have been limited to analyses of functional activity. Here we examined the effects of cortical atrophy on conceptual combination and found that angular-gyrus atrophy results in impaired comprehension of combined concepts relative to single-word concepts. However, it can be argued that processing two words is more challenging than processing single words, and thus our difference score might reflect general task difficulty. However, if the contribution of the angular gyrus reflects general task demands, one would expect the low-combinatorial items in our fMRI study to elicit the strongest activation, which is the opposite of the observed fMRI effect. Altogether, the

most consistent account for our findings is that the angular gyrus supports the comprehension of combined concepts.

Research on conceptual combination has been framed in a number of different ways in the literature. One line of investigation has focused on the processing of semantically ambiguous or anomalous phrases (also referred to as semantic integration). For example, the N400 effect in electrophysiological studies is strongly elicited by words that are unexpected given the preceding context (e.g., “I like my coffee with cream and socks”) (Kutas and Hillyard, 1980; Kutas and Federmeier, 2000). These effects are often thought to reflect a mechanism for integrating the meaning of a word with the preceding semantic context, where more unification is elicited by increasingly unexpected words (Hagoort, 2005). An alternative interpretation has been that lexical access to the target word is made more challenging by the incongruent context and thus increased effort is required (Lau et al., 2008). Our experiments and recent studies from other groups have begun to examine the mechanisms involved in fluent conceptual combination in language, in which basic conceptual constituents are integrated coherently into higher-level representations (Graves et al., 2010; Bemis and Pylkkänen, 2011). Although each of these approaches focuses on a different cognitive process, they are all relevant to understanding the full spectrum of conceptual combination. We suggest that the differences in current theoretical frameworks partly reflect the lack of an established taxonomy for the cognitive processes in conceptual combination, rather than fundamental differences in what constitutes conceptual combination.

In this series of studies we analyzed conceptual combinations via a lexical modality of input. However, considering these findings in light of other work it seems likely that the semantic information in the angular gyrus is independent of the material of



input (e.g., lexical, pictorial). Indeed, a recent study by Fairhall and Caramazza (2013) showed that the angular gyrus is one region that can successfully cross-classify between visual objects and their corresponding single-word representations (e.g., between the word “apple” and a picture of an apple). Future work is needed in order to explicitly characterize whether the combinatorial mechanisms in this region are independent of the lexical and pictorial material used to access conceptual information.

Across many studies of lexical-semantics the angular gyrus has been implicated bilaterally in lexical-semantic processing (Binder et al., 2009; Bonner et al., 2013). Our results are also consistent with a bilateral contribution, although there may be subtle hemispheric differences. Our fMRI results demonstrate that combinatorial processing modulates activity in both the left and right angular gyri. Indeed, activity in the left and right angular gyri did not differ and were highly correlated in our item analysis. Furthermore, in the patient analysis the degree of atrophy in *both* the left and right angular gyri correlated with impaired combinatorial processing. However, when we examined individual differences in combinatorial processing across healthy adults within the structural MRI analysis, we found that the strongest structure-function relationship was in the right angular gyrus, with no indication of a similar relationship in the left hemisphere. With typical left hemisphere language dominance in right-handers, lexical-semantic processing may rely more consistently on the left angular gyrus across subjects for all types of combinatorial stimuli. However for some participants, an advantage may be gained by additionally recruiting the right angular gyrus and thus, the right angular gyrus may be more sensitive to individual differences across subjects in lexical-semantic processing (Heim et al., 2010).

In conclusion, we have shown in a series of experiments that the neural

mechanisms for conceptual combination rely on the heteromodal association cortex of the angular gyrus. We found that activity in the angular gyrus is modulated by conceptual combination in healthy adults, and that combinatorial performance is sensitive to the degree of angular gyrus atrophy in patients. These converging findings indicate that the angular gyrus plays a critical role in integrating semantic information.

## CHAPTER 3

### **Causal evidence for a mechanism of semantic integration in the angular gyrus as revealed by high-definition transcranial direct current stimulation (HD-tDCS)**

Amy R. Price, Jonathan E. Peelle, Michael F. Bonner, Murray Grossman, and Roy Hamilton. *Journal of Neuroscience*, 2016.

#### **ABSTRACT**

A defining aspect of human cognition is the ability to integrate conceptual information into complex semantic combinations. For example, we can comprehend “plaid” and “jacket” as individual concepts, but we can also effortlessly combine these concepts to form the semantic representation of “plaid jacket”. Many neuroanatomic models of semantic memory propose that heteromodal cortical hubs integrate distributed semantic features into coherent representations. However, little work has specifically examined these proposed integrative mechanisms and the causal role of these regions in semantic integration. Here, we test the hypothesis that the angular gyrus is critical for integrating semantic information by applying high-definition transcranial direct current stimulation (tDCS) to an fMRI-guided region of interest in the left angular gyrus. We found that anodal stimulation to the left angular gyrus modulated semantic integration but had no effect on a letter-string control task. Specifically, anodal stimulation to the left angular gyrus resulted in faster comprehension of semantically meaningful combinations like “tiny radish” relative to non-meaningful combinations like “fast blueberry.” This effect was not observed during sham stimulation or stimulation to a control region. Moreover, the size of the effect from brain stimulation correlated with the degree of semantic

coherence between the word pairs. These findings demonstrate that the left angular gyrus plays a causal role in the integration of lexical-semantic information, and that high-definition tDCS to an associative cortical hub can selectively modulate integrative processes in semantic memory.

### **SIGNIFICANCE STATEMENT**

A major objective in neuroscience is to understand the neural basis of behaviors that are fundamental to human intelligence. One essential behavior is the ability to integrate conceptual knowledge from semantic memory, allowing us to construct an almost unlimited number of complex concepts from a limited set of basic constituents (e.g., “leaf” and “wet” can be combined into the more complex representation “wet leaf”). Here, we present a novel approach to studying integrative processes in semantic memory by applying focal brain stimulation to a heteromodal cortical hub implicated in semantic processing. Our findings demonstrate a causal role of the angular gyrus in semantic integration and provide motivation for novel therapeutic applications in patients with lexical-semantic deficits.

## INTRODUCTION

The human brain can construct an almost unlimited number of conceptual combinations from a finite set of constituents (e.g., creating “soft plaid jacket” from the constituents “soft”, “plaid”, and “jacket”). The cognitive aspects of semantic composition have been debated for hundreds of years in philosophy, linguistics, and psychology (Hume, 1739/1978; Wernicke, 1874; Dejerine, 1892; Wittgenstein, 1953; Geschwind, 1965; Fodor, 1975; Murphy, 2002), and in recent decades neuroscientists have begun to develop models for how the brain might carry out these combinatorial processes in semantic memory.

Many models of semantic memory include the idea of “hubs” or “convergence zones” for semantic information. These hubs are proposed to have two key features: 1) they are amodal or multimodal in nature, because they represent information across multiple sensory modalities (e.g., auditory and visual knowledge); and 2) they are integrative, in that they store high-level information about the associations between features of concepts. Although recent work has begun to characterize the amodal nature of semantic hubs (Devereux et al., 2013; Fairhall and Caramazza, 2013), few studies have directly tested their integrative functions in semantic memory or provided causal evidence for how the brain carries out these integrative processes.

Findings from fMRI and MEG have suggested that one potential hub for semantic-memory integration is the angular gyrus (Vigneau et al., 2006; Binder et al., 2009; Graves et al., 2010; Bemis and Pylkkänen, 2013; Price et al., 2015d). Indeed, the anatomic properties of this region are indicative of high-level multimodal processing. The angular gyrus is a heteromodal brain region in the inferior parietal lobe with reciprocal

white-matter connections to sensorimotor cortices as well as classic language regions in the inferior frontal and superior temporal gyri (Caspers et al., 2011). Heteromodal cortices like the angular gyrus also have larger and more complex dendritic fields relative to unimodal cortices, suggestive of diverse and highly integrative computations (Elston et al., 2001; Jacobs et al., 2001).

In this study, we directly tested the integrative role of the left angular gyrus in semantic memory by applying high-definition transcranial direct-current stimulation (HD-tDCS) (Datta et al., 2009) in healthy adults to modulate neural activity and determine its effects on semantic integration. HD-tDCS is a recent innovation in brain-stimulation technology that allows for the application of relatively focal current stimulation by using a circumscribed array of scalp electrodes. The multi-electrode array allows for anatomic specificity that is not possible with traditional tDCS (Datta et al., 2009; Caparelli-Daquer et al., 2012; Kuo et al., 2013). Preliminary evidence suggests that the effects from HD-tDCS may be larger and longer lasting than conventional tDCS (Kuo et al., 2013).

Here, we applied anodal HD-tDCS to our brain regions of interest. Anodal stimulation is associated with cortical excitability (Nitsche and Paulus, 2000, 2001; Antal et al., 2004) through incremental depolarization of the resting membrane potential and increased neural firing rates (Bindman et al., 1964; Purpura and McMurtry, 1965). tDCS has been widely used to better understand causal brain-behavior relationships in many cognitive domains (Nitsche et al., 2003; Floel et al., 2008; Cohen Kadosh et al., 2010; Turkeltaub et al., 2012; Ruff et al., 2013; Filmer et al., 2014; Reinhart and Woodman, 2015), and recent work has shown reliable effects of left-hemisphere anodal tDCS on language performance (Price and Hamilton, 2015b; Price et al., 2015c).

To examine causal relationships between the angular gyrus and lexical-semantic integration, we administered HD-tDCS while participants performed a two-word comprehension task. Participants underwent three separate brain-stimulation sessions: left angular gyrus, right angular gyrus, and sham stimulation. We also administered a letter-string task to test for more general effects on attention and visual processing. Like many language functions, lexical-semantic processing appears to be relatively left lateralized in right-handed participants (Binder et al., 2009; Price et al., 2015d). Thus we hypothesized that anodal stimulation to the left angular gyrus would selectively modulate integrative processes in semantic memory, resulting in faster reaction times for the comprehension of meaningful adjective-noun combinations.

## **MATERIALS AND METHODS**

### **Participants**

A total of 18 healthy adults from the University of Pennsylvania community participated in the study (9 female, mean age = 25.3 years, age range 20-39 years). In a within-subjects design, each participant completed three separate brain-stimulation sessions, for a total of 54 sessions. All participants were native English speakers, right-handed (as assessed by the Edinburgh Handedness Inventory), and had normal or corrected-to-normal vision. Participants had no history of neurological difficulty or preconditions (e.g., epileptic seizures, brain injuries, implants), or psychiatric illness, as determined by a pre-experiment screening. We obtained informed consent from all participants according to a protocol approved by the University of Pennsylvania Institutional Review Board.

## **Experimental Procedure**

The experimental instructions were identical for all sessions. In a within-subjects design, participants received the three separate brain-stimulation conditions with their order counterbalanced across participants: (1) a left angular gyrus anodal stimulation condition, (2) a right angular gyrus anodal stimulation condition, (3) a sham stimulation condition (see HD-tDCS application section for the placement of electrodes). The sessions were scheduled at the same time of day for each participant and they were a minimum of 48 hours apart to avoid potential carryover effects from stimulation.

## **HD-tDCS application**

### *Current delivery*

The current was generated by a NeuroConn DC Stimulator Plus channeled through a 4x1 multichannel stimulation device (Soterix Medical). For the active anodal brain-stimulation sessions, a constant current of 2.0 mA was delivered for a period of 20 minutes, preceded and followed by linear ramp-up and ramp-down periods of 30 seconds in order to minimize mild discomfort felt during the beginning and end of stimulation. For the sham stimulation session, a constant current of 2.0 mA was delivered for a period of 30 seconds preceded and followed by the same linear ramp-up and ramp-down periods of 30 seconds (to induce the initial tingling sensations of current flow felt in the active stimulation conditions), and then followed by 19.5 minutes of no stimulation. Thus the stimulation protocol for each session lasted 21 minutes. Because effects of HD-tDCS last for up to 2 hours post stimulation (Kuo et al., 2013), this protocol



allowed us to conduct behavioral testing after stimulation but yet still during the period of neural alteration.

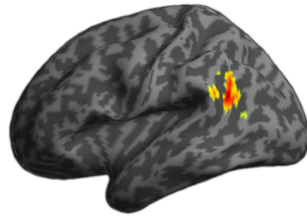
#### *HD-tDCS 4x1 ring design*

The HD-tDCS ring design has been shown to replicate classic findings from conventional tDCS, using a 1x1 saline-soaked sponge electrode montage, while producing better spatial focality and a potentially longer lasting aftereffect than conventional tDCS (Datta et al., 2009; Caparelli-Daquer et al., 2012; Kuo et al., 2013). While HD-tDCS is associated with stronger scalp sensations than conventional tDCS, it has been shown to be safe and tolerable with applications of up to 2.0 mA for 20 minutes (Minhas et al., 2010; Borckardt et al., 2012; Kuo et al., 2013).

Five sintered Ag/AgCl ring electrodes (outer diameter: 12 mm, inner diameter: 6 mm; Stens Biofeedback) were used for the 4x1 ring design. One anode was placed directly over the stimulation site, and surrounded by four equally spaced cathodes at a radius of approximately 6 cm from the anode (Figure 7B). The five electrodes were connected to the four-to-one wire adaptor for the DC stimulator (NeuroConn DC Stimulator Plus), a battery-driven stimulator that generated the direct current. This 4x1 design allows for focal delivery of anodal current to the targeted brain region using a constant current of 2.0 mA while applying weaker cathodal current since it is split by a factor of four. The electrodes were stabilized by plastic electrode holders (customized from Soterix Medical; radius ~1 cm) in a fitted cap (EASYCAP). The holders were filled with SignaGel, creating a gel contact of 3.1 cm<sup>2</sup> per electrode. We tailored the stimulation montages to target our brain regions of interest by generating theoretical models of current flow using the HD-Explore™ software (Soterix Medical Inc.), which

uses a finite-element-method (FEM) modeling approach to quantify electric field intensity throughout the brain (Figure 7C) (Datta et al., 2009; Dmochowski et al., 2011; Kempe et al., 2014). The locations of the electrodes were chosen by selecting the 10-20 EEG sites across the participants that would optimally target a region in the left angular gyrus identified in a previous fMRI study using a similar task to examine combinatorial semantics in healthy adults (Price et al., 2015d). The peak coordinates from this study were: -52 -56 22 (MNI coordinates), which served as the target for our left angular gyrus montage. We also targeted the corresponding contralateral coordinates for our right angular gyrus montage: 52 -56 22 (MNI coordinates). The peak coordinates for the left angular gyrus come from a whole-brain random-effects t-test of meaningful minus non-meaningful word pairs. Thus this corresponds to the region showing the most consistently strong effect across subjects. Furthermore, this peak falls within PGa, a subregion of the angular gyrus, as defined by cytoarchitectonic parcellation (Caspers et al., 2006; Caspers et al., 2008). For the left angular gyrus session, this resulted in selecting the central anode as CP5 in the 10-20 EEG coordinate system, and surrounding it by four cathode electrodes at C3, T7, P7, and P3 (forming a distance of approximately 6 cm from the central electrode). For the right angular gyrus session, a mirror coordinate montage was designed such that the central anodal electrode was placed at CP6 in the 10-20 EEG coordinate system and surrounded by four cathodal return electrodes at C4, T8, P8, and P4. For the sham condition, we counterbalanced whether we placed the electrodes in the left or right angular gyrus configuration.

**A. fMRI Results**

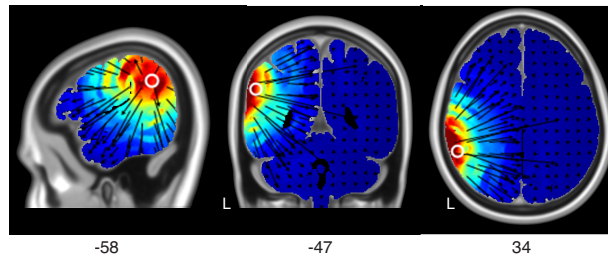


**B. Electrode placement**

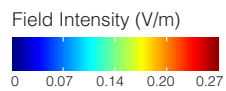
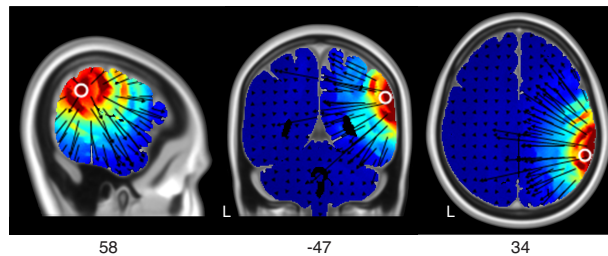


**C. Current modeling**

Left angular gyrus electrode montage



Right angular gyrus electrode montage



**Figure 7.** Experimental design (A) Left angular gyrus fMRI activation in healthy adults for the processing of meaningful relative to non-meaningful word pairs (Price et al., 2015d). (B) Example placement of electrodes and electrode holders for the HD-tDCS 4x1 configuration. (C) Theoretical models of the electric field intensity for the electrode montages targeting the left angular gyrus and right angular gyrus (HD-Explore™, Soterix Medical Inc.)

## **Materials**

### *Stimuli for the word-pair task*

Aspects of the stimulus design for the word-pair task were adapted from a previous study, which showed that activity in the left angular gyrus was modulated by the degree to which a word pair formed a meaningful conceptual combination (Price et al., 2015d). For the current study, a larger number of stimuli were developed in order to create three separate stimulus sets that would allow us to test behavior across three separate brain stimulation sessions. There were no word repetitions across the stimulus sets, which allowed us to avoid confounds of familiarity and repetition effects across testing sessions. Using a similar approach to stimulus design as in Price et al. (2015d), the word pairs for this study were designed to systematically vary in how readily the two words could be integrated into a semantically coherent combination (as determined in a series of norming studies, described below). The word pairs consisted of those that readily combined to form semantically coherent combinations (e.g., “tiny radish” or “plaid jacket”), which we refer to as meaningful combinations, and pairs that did not readily combine to form semantically coherent combinations (e.g., “fast blueberry” or “stretchy frost”), which we refer to as non-meaningful combinations, illustrated in Figure 8A. All word pairs, both meaningful and non-meaningful, were adjective-noun word pairs.

To develop the stimuli, we created a corpus of over 400 word pairs and collected norming data that included reaction time, plausibility ratings, orthographic neighborhood density (Medler and Binder, 2005), number of syllables, letter length, average log lexical frequency from the Subtlexus database (Brysbaert and New, 2009), average log single word frequency from Google, and log co-occurrence word frequency from Google.

Google co-occurrence frequency was determined by counting the number of times the two words occurred together in a particular order within all web pages ending in “.com” that are indexed on Google (i.e., assessing unidirectional co-occurrence, which is how frequently the words “plaid jacket” occur together in sequence, but not counting the reverse sequence “jacket plaid”). Specifically, we identified the number of search hits for each word pair and took the log of this value to generate the log co-occurrence frequency. The process was similar for determining the single word frequency using Google, except that it was the log of the number of hits for that individual word instead of the pair of words. In a separate norming study ( $n = 24$  healthy adults), we collected two sets of data on all word pairs: a meaningfulness yes/no task, as well as plausibility ratings of the stimuli using a 1-to-7 scale. In the meaningfulness yes/no task subjects were asked to decide whether each word pair formed a meaningful combination or not. Using these yes or no responses, we retained all word pairs with more than 85% agreement across subjects, and we then split the retained stimuli into “meaningful” and “non-meaningful” categories based on subjects’ responses (i.e., yes = meaningful combination, no = non-meaningful combination). These word pairs were then submitted to a stimulus-optimization algorithm implemented in the MATCH software (Van Casteren and Davis, 2007) in order to select subsets of meaningful and non-meaningful word pairs that were best matched on a large number of psycholinguistic variables.

Using MATCH we created a total of six sets of stimuli: two categories (meaningful and non-meaningful word pairs) by three stimulation sessions, creating a total of 210 stimuli used across all three stimulation sessions (35 meaningful and 35 non-meaningful for each of the three session). The stimulus sets were designed to match on specific variables across sessions and word-pair categories (e.g., single word

frequency) while differing on other variables between word-pair categories (e.g., plausibility ratings). Thus each word-pair category was optimally matched across sessions on reaction time on the meaningful yes/no norming task (all p values > 0.44), plausibility ratings (all p values > 0.41), average word frequency from Subtlexus (all p values > 0.58), average word frequency from Google (all p values > 0.40), co-occurrence word frequency from Google (all p values > 0.64), orthographic neighborhood density (all p values > 0.70), letter length (all p values > 0.22), and syllable number (all p values > 0.51). The meaningful and non-meaningful word-pair categories were designed to significantly differ across sessions on plausibility ratings (all p values < 0.001) and co-occurrence frequency (all p values < 0.001). Indeed, there was no overlap in average plausibility ratings between any of the words pairs in the two categories (i.e., the range of plausibility values for all meaningful word pairs was 5.54 to 7.00, while the range of the plausibility values for all of the non-meaningful word pairs was 1.00 to 2.54). The pairing of each set of stimuli with each stimulation condition was then counterbalanced across participants.

In addition to being able to divide the word pairs categorically into meaningful and non-meaningful word-pair categories, all three sets of meaningful words pairs were systematically designed to include the same range, distribution, and mean plausibility values based on the norming study (set 1 range = 5.54 to 7, set 1 mean = 6.63, set 1 SD = 0.35; set 2 range = 5.75 to 7, set 2 mean = 6.63, set 2 SD = 0.28; set 3 range = 5.67 to 7, set 3 mean = 6.56, set 3 SD = 0.33). These plausibility ratings were used as a continuous measure of semantic coherence, which we used in an item analysis of the stimulation effects on individual word pairs (described in the data analysis section below).

In a separate training task, participants viewed word pairs from a well-controlled published corpus (Graves et al., 2013) containing noun-noun word pairs that were designed in a similar manner to the adjective-noun word pairs in this study. We filtered all 2,160 word pairs from Graves et al. (2013) for words used in any of the tasks in our study, such that no word would be repeated in subsequent experimental tasks. The same training set was used in all three stimulation sessions.

### **Task Procedure**

The presentation and timing of the stimuli were controlled using E-prime version 2 (Psychology Software Tools). The tasks were carefully timed and presented in the same order across all stimulation sessions. Before each session, participants completed practice versions of the word-pair and letter-string tasks with feedback to ensure that they understood the tasks. We then administered the stimulation protocol. During stimulation, subjects performed the training task using stimuli from Graves et al. (2013). This training task began ten minutes after the onset of stimulation to allow for subjects to adjust to the scalp sensations of HD-tDCS. The training task lasted six minutes. Immediately after the stimulation period ended, participants began the experimental tasks, which started with the word-pair task and was then immediately followed by the letter-string task (each experimental task lasted approximately 5 minutes). Participants were instructed to indicate their answer as quickly as possible for both the word-pair task and the letter-string task. For a separate study, participants also completed a recognition memory task at the end of the experiment, which is not examined here.

### *The word-pair task*

Participants were instructed to use their right hand for all tasks and to press one button if the displayed adjective-noun word pair formed a meaningful combination (e.g., “tiny radish”) and another button if it did not (e.g., “fast blueberry”). On each trial, a fixation cross was presented for 500 ms before the onset of the word pair. Subjects read the word pair and indicated their answer by button press. Their response ended the trial and moved the subject to the beginning of the fixation cross of the next trial. Stimulus order was randomized for each participant. For each session, there were a total of 70 word-pair trials (35 meaningful and 35 non-meaningful combinations), with 10 randomly distributed null events (3 seconds in duration). Thus across all three sessions, there were 210 unique word-pair trials with no word repetitions within or across sessions.

### *The letter-string control task*

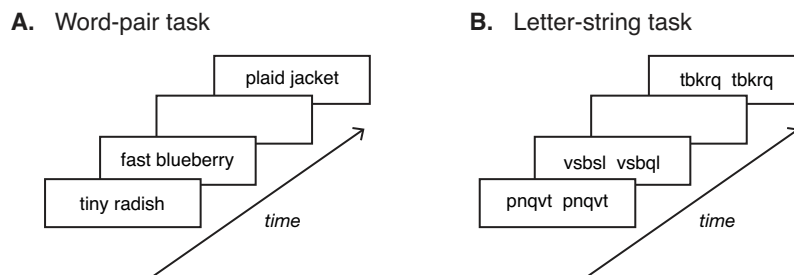
The letter-string task was designed to serve as a general control task for vision and attention. In this task, non-pronounceable letter strings were displayed on the screen and participants were asked to make small visual discriminations between the pairs of letter strings, illustrated in Figure 8B. Participants were asked to respond using the same button responses as the word-pair task and to indicate whether or not the letter strings matched (e.g., pnqvt pnqvt) or not (e.g., vsbsl vsbql). The letter strings were always composed of 5 consonants, and non-match letter strings differed by one letter. Subjects viewed the letter strings and indicated their answer by button press. Their response ended the trial and moved the subject to the beginning of the fixation cross of the next trial. Stimulus order was randomized for each participant. For each session, there were a total of 70 letter-string trials (half matched and half did not) and 10 random null events (3



seconds in duration). As with the word-pair task, there were never any repetitions of stimuli within or between sessions, and the stimulus sets was counterbalanced across participants. Thus across all three sessions, there were 210 unique letter-string trials.

### *Scalp sensation and discrimination of sham in HD-tDCS*

At the end of each session, participants evaluated their sense of discomfort during the session by using a visual analog scale (ranging from 0 to 10) for the sensations of tingling and burning. After the participant had completed all three sessions of the study, they were asked to guess whether they thought that they had received sham or real stimulation in each session.



**Figure 8.** Behavioral tasks and example stimuli (A) In the word-pair task, participants viewed two real words whose combination was considered to be either meaningful (e.g., tiny radish) or non-meaningful (e.g., fast blueberry), as determined by the results of a norming study. On each trial, participants were asked to decide whether the word pair formed a meaningful combination or not. (B) In the letter-string control task, participants viewed two letter strings that were either the same letter strings (e.g., pnqvt pnqvt) or differed by one letter (e.g., vsbsl vsbql). On each trial, participants were asked to decide whether the letter strings matched or not.

## Data Analysis

### *Random-effects analyses on the categories of word pairs and letter-string pairs*

For each participant, we analyzed the mean reaction time and mean accuracy for each category in the word-pair task and letter-string task, summarized in Table 3. For the reaction time analyses, we had specific hypotheses about the changes in reaction time across sessions for each task. We hypothesized that there would be a larger combinatorial processing advantage in the left angular gyrus session relative to the sham and the right angular gyrus session. To examine this specific combinatorial processing change, we used a difference score between our meaningful and non-meaningful word-pair categories (e.g., meaningful RT minus non-meaningful RT), which is robust to overall performance differences across testing days and which provides a specific test for differential effects related to the semantic coherence of the word-pair combinations. We performed paired-sample t-tests for the planned comparisons of reaction time difference scores between stimulation conditions. The same analysis was conducted for the letter-string task (e.g., matching letter strings RT minus non-matching letter strings RT). Since we had hypothesized directions of effects for these comparisons, these t-tests were one-tailed.

We next examined an alternative analysis to the difference score. Since the sham stimulation condition can be thought of as a baseline condition, we also examined stimulation effects as a function of the percentage change relative to sham stimulation for each of the real stimulation conditions. Specifically, for each subject we calculated the percentage change in reaction time for real stimulation (i.e., left and right angular gyrus stimulation) relative to sham stimulation for the meaningful and non-meaningful

word-pair categories separately. For example, the percentage change of the meaningful category in the left angular gyrus session was calculated in the following way:  $(RT_L - RT_S) / RT_S$ , where  $RT_L$  is reaction time for the meaningful category in the left angular gyrus session and  $RT_S$  is reaction time for the meaningful category in the sham session.

At the end of the last session, one participant reported that he had little-to-no sleep the night before and felt sleepy during testing. We performed an outlier analysis to determine whether the data for this participant or any other participant were unusual and potentially disproportionately affecting the reaction time results. For each participant, we calculated their variation coefficient (i.e., an inverse signal-to-noise ratio) by taking the standard deviation (SD) in reaction time across sessions and dividing it by the mean reaction time. This score provides a measure of how variable a participant's performance is across testing sessions, with higher values indicating greater variability. The participant who reported feeling sleepy had a variation coefficient that was greater than 3.5 standard deviations away from the mean across participants. The variation coefficients of all other participants were less than 1 standard deviation away from the mean. We therefore removed this outlier participant from the analyses. However, we note that including this participant does not affect the significance of any of the statistical analyses reported in this study because this person showed an effect in the hypothesized direction for each of the analyses (all p values < 0.05 for any significant comparison reported in the results section; all non-significant comparisons remain non-significant).

### *Item analysis of individual word pairs*

We performed item-level analyses in order to examine graded effects from stimulation to individual word pairs in the meaningful category. A traditional item analysis examines the effect on each stimulus item by performing random-effects analyses across items in the experiment instead of across subjects (Clark, 1973). Because we could not repeat the same exact words across stimulation sessions (in order to avoid repetition effects), our first item-level analysis was designed to compare words pairs of the same *rank* across sessions. We followed this with an ANCOVA using the actual item-level metrics instead of ranks.

The use of ranks in the first item analysis allowed us to examine stimulation effects at individual levels of semantic coherence. This approach assumes that corresponding ranks reflect similar semantic coherence values across stimulus sets. As described in the stimulus materials section, the design of our experimental stimuli involved systematically varying the semantic coherence (i.e., the plausibility ratings of the combinations) across the word pairs in the meaningful category in three sets of stimuli. We performed extensive norming to create word pairs between sets that were highly matched on semantic coherence on an individual basis, such that item ranks could be used to compare levels of semantic coherence across stimulus sets while avoiding repetition confounds. Indeed, the semantic coherence values for word pairs with corresponding ranks were nearly identical. We quantified how similar they were by taking the average absolute difference of semantic coherence values for all pairwise comparisons of items with the same rank across the three stimulus sets. The mean absolute difference in semantic coherence values for stimuli of the same rank was 0.067 (SD = 0.045), which was 1.19% of the mean semantic coherence of all meaningful word

pairs. Additionally, the average correlation coefficient between all pairwise correlations of semantic coherence values across the sets is almost 1 (i.e., set 1 to set 2 correlation:  $r = 0.99$ ; set 1 to set 3 correlation:  $r = 0.98$ ; set 2 to set 3 correlation:  $r = 0.98$ ). Furthermore, these sets were counterbalanced across stimulation sessions, such that each set was run equally for each type of brain stimulation condition.

Thus to perform this item analysis, the meaningful word pairs were ranked by their semantic coherence values for each session for all subjects. Using ranked semantic coherence allowed us to look at changes in reaction time for individual items, by averaging across participants' reaction time data for the same ranked word pairs in each stimulation condition and then taking the difference in reaction time for items of the same rank in different stimulation sessions (e.g., reaction time for left angular gyrus word pair rank 1 minus reaction time for sham word pair rank 1; where negative values indicate an advantage gained by left angular gyrus stimulation relative to sham stimulation). We then performed two-tailed correlations across the ranked items to test for graded differential effects to the word pairs from stimulation.

To ensure that the effects from the item-analysis above were not solely driven by the use of ranks instead of the actual semantic coherence metrics for each item in the meaningful category, we performed an analysis of covariance (ANCOVA) using the exact semantic coherence values for each item, with a dependent variable of reaction time and independent variables for subject (random), stimulation condition (fixed), and semantic coherence values (random).

Stimulation condition	Word-pair task					Letter-pair task				
	Reaction time, ms: meaningful word pair	Reaction time, ms: non-meaningful word pair	Combinatorial processing RT difference, ms	Accuracy, %: meaningful word pair	Accuracy, %: non-meaningful word pair	Reaction time, ms: match letter pair	Reaction time, ms: non-match letter pair	Letter-task processing RT difference, ms	Accuracy, %: match letter pair	Accuracy, %: non-match letter pair
Left AG	1033.9 ± 44.4	1059.2 ± 44.9	-25.2 ± 22.1	91.8 ± 1.8	98.7 ± 0.5	1510.9 ± 75.9	1392.4 ± 50.2	118.5 ± 38.1	97.8 ± 0.6	96.8 ± 1.0
Right AG	1118.8 ± 58.1	1037.6 ± 36.2	81.3 ± 45.0	90.9 ± 1.6	99.3 ± 0.3	1604.7 ± 83.8	1470.5 ± 72.5	134.2 ± 33.6	98.2 ± 0.5	94.8 ± 1.0
SHAM	1077.4 ± 64.5	1029.0 ± 48.2	48.4 ± 33.4	90.8 ± 1.9	99.3 ± 0.3	1565.8 ± 77.4	1408.2 ± 48.4	157.5 ± 36.5	97.6 ± 0.7	96.0 ± 1.0

Values listed are the mean ± SE of reaction time (ms) or accuracy (%) for each stimulation condition and task.

**Table 3.** Reaction time and accuracy from the word-pair and letter-string tasks

## RESULTS

Participants were unable to distinguish the sham session from real tDCS above chance level ( $p = 0.77$ , proportions test), demonstrating that the HD sham protocol was effective at blinding the participants to the sham session. There were no differences in ratings of tingling sensations (average tingling sensation = 2.45, SD = 2.51;  $F(2,32) = 1.06$ ,  $p = 0.36$ , one-way repeated measures ANOVA), or in ratings of burning sensations (average burning sensation = 2.14, SD = 2.26;  $F(2,32) = 2.1$ ,  $p = 0.14$ ) between stimulation conditions.

Based on the norming study, we expected participants' accuracy to be highly accurate on both tasks for all sessions. To test for possible accuracy changes across sessions in each task, we conducted a repeated measures analysis of variance (ANOVA) for accuracy by stimulation condition. Participants were highly accurate and close to ceiling at both the combinatorial word-pair task (average accuracy = 95.1%, SD = 2.8%) and the letter-string control task (average accuracy = 96.9%, SD = 2.0%). There

was no effect of stimulation on accuracy in the combinatorial word-pair task ( $F(2,32) = 0.01$ ,  $p = 0.99$ ). There was no effect of stimulation on accuracy in the letter-string control task ( $F(2,32) = 0.76$ ,  $p = 0.48$ ).

In the first set of reaction-time analyses, we examined the performance advantage in the word-pair task and letter-string task across subjects. Next, we examined the specific effects on individual word pairs in the meaningful word-pair category.

### **Reaction time effects on categories in each task: Random-effects across participants**

For the reaction time analyses, we hypothesized that stimulation to the left angular gyrus would produce a greater processing advantage for meaningful relative to non-meaningful word pairs when compared with the other stimulation conditions (i.e., sham and right angular gyrus). If the left angular gyrus encodes high-level associative information from multiple lexical-semantic inputs, then stimulation to the left angular gyrus should specifically facilitate the representation of meaningful combinations, which have more abundant semantic associations than the non-meaningful combinations. Furthermore, we expected that if there were any effect on non-meaningful word pairs, it would be in the opposite direction because left angular gyrus stimulation might elicit spurious semantic associations for these word pairs.

In the word-pair task, a repeated-measures ANOVA of stimulation condition (left AG, right AG, and sham) by word-pair category (meaningful and non-meaningful) showed no main effect of word-pair category ( $F(1,16) = 1.90$ ,  $p = 0.19$ ), no main effect of stimulation condition ( $F(2,32) = 0.91$ ,  $p = 0.41$ ), and a trending interaction of word-pair

category and stimulation condition ( $F(2,32) = 3.09, p = 0.059$ ). We next performed planned comparisons to test our primary experimental hypothesis. As explained in the Data Analysis section, we examined direct comparisons of the difference scores for the word-pair categories across stimulation conditions to test for changes in the relative processing advantage of meaningful combinations (Figure 9A-B). As hypothesized, we found that anodal stimulation to the left angular gyrus resulted in a greater processing advantage for meaningful relative to non-meaningful word pairs when compared with both sham stimulation ( $t(16) = 1.96, p = 0.03$ ) and right angular gyrus stimulation ( $t(16) = 1.91, p = 0.04$ ), shown in Figure 9A.

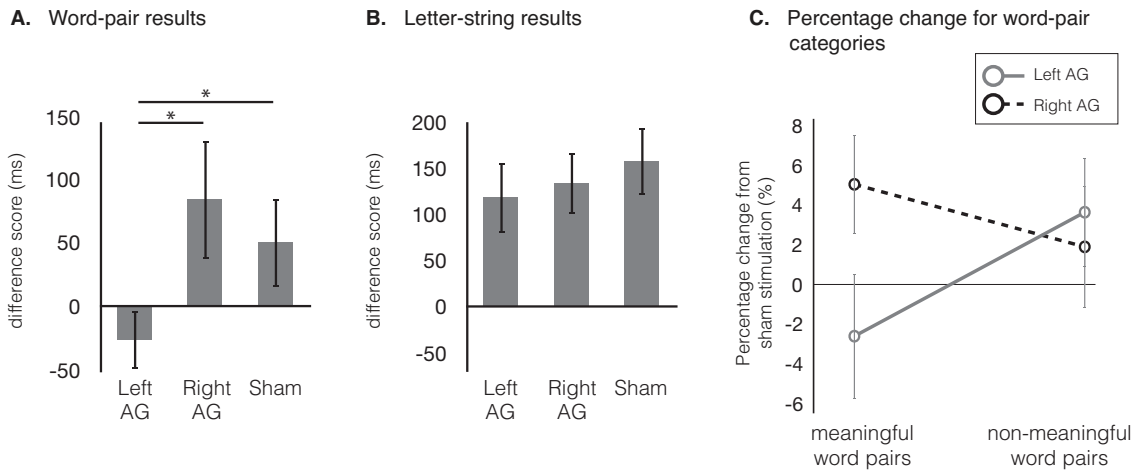
In the letter-string task, a repeated-measures ANOVA of stimulation condition (left AG, right AG, and sham) by letter-string category (match and non-match) showed a main effect of letter-string category ( $F(1,16) = 18.9, p < 0.001$ ), no main effect of stimulation condition ( $F(2,32) = 1.79, p = 0.18$ ), and no interaction between letter-string category and stimulation condition ( $F(2,32) = 0.66, p = 0.52$ ). We next performed direct comparisons of difference scores for the letter-string categories across stimulation conditions. These analyses showed no differential effects in the processing of letter-string categories across any of the stimulation conditions (all  $p$  values  $> 0.25$ ), shown in Figure 9B.

To further quantify the effect of real versus sham stimulation on each word-pair category, we examined the percentage change in reaction time relative to sham, plotted in Figure 9C. The use of percentage change has the benefit of normalizing effects within each subject relative to a baseline measure. A repeated-measures ANOVA showed no main effect of word pair category ( $F(1,16) = 0.71, p = 0.41$ ), no main effect of stimulation condition ( $F(1,16) = 2.39, p = 0.14$ ), and a trending interaction between word-pair



category and stimulation condition ( $F(1,16) = 3.83, p = 0.068$ ). As expected, a direct comparison between the percentage change for the meaningful word pairs revealed a significant difference between the left and right angular gyrus stimulation sessions ( $t(16) = 2.48, p = 0.01$ ), whereas there was not a significant difference for the non-meaningful word pairs between left and right angular gyrus stimulation sessions ( $t(16) = 0.57, p = 0.29$ ). When we performed the percentage-change analysis on the letter-string task, a repeated-measures ANOVA showed no main effect of letter string category ( $F(1,16) = 2.15, p = 0.16$ ), no main effect of stimulation condition ( $F(1,16) = 1.63, p = 0.22$ ), and no interaction between letter-string category and stimulation condition ( $F(2,32) = 0.08, p = 0.78$ ).

These results demonstrate anatomic specificity across participants: this effect was specific to anodal stimulation of the left angular gyrus, and did not occur for the sham condition or the anodal right angular gyrus condition. Furthermore, stimulation produced this effect in the word-pair task but not in the letter-string task.



**Figure 9.** Reaction time results from both tasks (A) Results from the word-pair task indicate a significant effect for the left angular gyrus stimulation session. For each session, the difference score was calculated as follows: average RT for meaningful word pairs - average RT for non-meaningful word pairs. Thus, negative values for the difference score indicate faster RT for the meaningful word-pair category relative to the non-meaningful word-pair category for that session. This reaction time difference score significantly differed between the left angular gyrus stimulation session and both the sham and right angular gyrus stimulation sessions ( $*p < 0.05$ ). (B) Results from the letter-string task indicate no effect of stimulation for any of the stimulation conditions (all  $p$ 's  $> 0.25$ ) (C) This plot shows the percentage change in reaction time for each word-pair category (mean  $\pm$  SE) in the left AG and right AG stimulation sessions relative to sham stimulation. Abbreviations: AG = angular gyrus.

### Reaction time effects on individual word pairs in the meaningful category:

#### Random-effects across word pairs

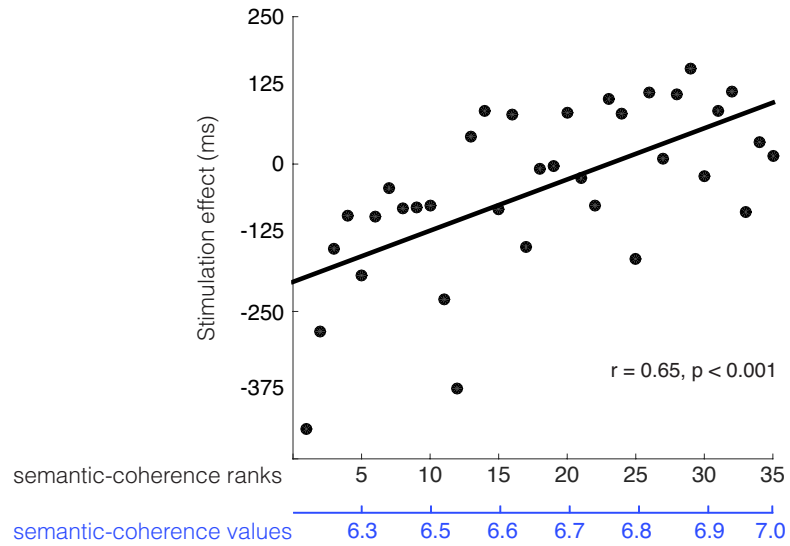
Next, we performed a series of item-level analyses to examine more fine-grained effects of how stimulation affected the meaningful word pairs on an individual basis. Specifically, we examined how the effects of stimulation related to the degree of semantic coherence across the meaningful word pairs. Using ranked coherence, we found that the change in reaction time between the left angular gyrus session and the sham session was strongly

correlated with the degree of semantic coherence of the word pairs ( $r = 0.65$ ,  $p < 0.001$ ), shown in Figure 10. This effect was not observed for the same item analysis comparing right angular gyrus to sham ( $r = 0.24$ ,  $p = 0.17$ ). To ensure that these results were not driven by differences in the items' reaction times at baseline (e.g. a 10% change would produce larger difference scores for items with larger reaction times at baseline), we performed the same analysis using relative changes in reaction time. The relative change in reaction time was calculated as the difference across testing sessions divided by the reaction time at baseline (i.e., in the sham session). The results for the left angular gyrus compared to sham condition remained strongly significant when using these normalized changes in reaction times ( $r = 0.62$ ,  $p < 0.001$ ).

We also performed an ANCOVA to test for an interaction of stimulation session and semantic coherence using the exact coherence values of each item instead of item ranks. Consistent with the findings from the item-rank analysis, we found a significant interaction of stimulation session and semantic coherence ( $F(2, 1763) = 7.73$ ,  $p < 0.001$ ).

Altogether, the item analyses shows that the effects from left angular gyrus stimulation were graded, such that the size of the effect was correlated with the degree of semantic coherence for the word pairs. More specifically, our results demonstrate that the performance gain from stimulation was greatest for the meaningful combinations that were the more challenging word pairs to integrate at baseline.

Item-analysis of individual word pairs



**Figure 10.** Results from the item analysis of individual word pairs from the meaningful word-pair category, illustrating the relationship between the size of the stimulation effect and the continuous measure of semantic coherence for the word pairs. The stimulation effect was calculated as the difference in mean reaction time between the left angular gyrus and sham stimulation sessions for word pairs of the same rank (i.e., RT for the left angular gyrus session minus RT for the sham session for each rank). The average semantic coherence values are listed below the ranks. Negative values indicate an advantage from left angular gyrus stimulation. The effect on RT from left angular gyrus stimulation strongly correlated with the degree of semantic coherence of the meaningful word pairs ( $r = 0.65, p < 0.001$ ).

## DISCUSSION

The angular gyrus has been proposed to function as a critical hub in the semantic memory system (Vigneau et al., 2006; Binder et al., 2009; Binder and Desai, 2011; Bonner et al., 2013; Seghier, 2013). However, it remains unclear whether the activation of this region reflects a specific integrative role in semantic memory, whether it could be attributed to other aspects of semantic processing, or whether it is epiphenomenal to semantic comprehension.

In this study, we tested the hypothesis that the left angular gyrus is an integrative region with a causal role in semantic comprehension by using HD-tDCS to apply anodal stimulation in three separate testing sessions. We found evidence that anodal stimulation to the left angular gyrus, but not the right angular gyrus or sham stimulation, modulated the processing of meaningful relative to non-meaningful two-word combinations during a comprehension task. Furthermore, there were fine-grained effects on individual word pairs within the meaningful category, with the size of the stimulation effect varying with a continuous measure of semantic coherence.

We found no effects in a letter-string control task, suggesting that the behavioral findings cannot be easily attributed to non-specific effects on attention, motor control, or low-level visual processing. It is important to note that the order of the word-pair and letter-string tasks was fixed across subjects. Effects from HD-tDCS have been found to last for up to two hours after the end of stimulation, making it unlikely that there were stimulation effects during the combinatorial task but not during the letter-string task. However this leaves open the possibility that the task-specific effects found here could be partially confounded with temporal effects of stimulation. Nonetheless, this issue does

not affect the interpretation of our main findings regarding the differential effects of angular gyrus stimulation across levels of semantic coherence.

### **Neurobiological properties of the angular gyrus**

Previous neuroimaging studies have implicated the angular gyrus in the process of building coherent representations from sequences of individual words (Graves et al., 2010; Lerner et al., 2011; Pallier et al., 2011; Bemis and Pykkänen, 2013; Price et al., 2015d). Our findings extend this previous work by showing that the angular gyrus is causally involved in constructing higher-level meaning from individual words during semantic comprehension, and that this process can be systematically manipulated using brain stimulation. The integrative process of conceptual combination relies on high-level conceptual associations acquired over years of experience. The idea that the angular gyrus encodes rich and highly abstract conceptual information acquired over large time scales aligns well with anatomic studies demonstrating that during postnatal development the inferior parietal cortex undergoes a pronounced expansion relative to unimodal sensory cortices (Hill et al., 2010). Furthermore, consistent with its role in high-level language processes, comparative anatomic studies suggest that this region has also undergone a prominent evolutionary expansion in humans relative to non-human primates (Orban et al., 2004; Van Essen and Dierker, 2007; Sherwood et al., 2008; Hill et al., 2010).

### **Hubs of the semantic memory network**

The stimulation protocol for this study was motivated by previous findings from an fMRI study (Price et al., 2015d). Our electrode montage was designed to optimize stimulation

at the peak coordinate from the fMRI study in the left angular gyrus. It will be of interest for future studies to explore the effects on combinatorial processing from application of HD-tDCS to other proposed hubs in the lexical-semantic network, which include the anterior temporal lobe (ATL) and the inferior frontal gyrus (IFG).

The ATL in particular has been implicated in a broad range of semantic-memory processes (Patterson et al., 2007; Visser et al., 2010; Schwartz et al., 2011), including conceptual combination (Baron et al., 2010; Bemis and Pylkkänen, 2011; Coutanche and Thompson-Schill, 2015). The most robust effects appear to be centered on ventromedial portions of the temporal lobe, such as the anterior fusiform and parahippocampal gyri (Mion et al., 2010; Bonner and Price, 2013; Bonner et al., 2016). Although HD-tDCS is useful for targeting lateral surfaces of the brain, it would be difficult to successfully target more ventromedial regions using HD-tDCS since current density decreases with increasing cortical depth (Datta et al., 2008; Datta et al., 2009; Faria et al., 2011). Additionally, using the 4x1 ring design would likely involve electrode placement on facial locations, which would pose problems due to high discomfort for participants and a less predictable flow of current.

It will be of interest in future work to understand how each of these high-level hubs of the semantic system work in concert to facilitate semantic integration (Molinaro et al., 2015). Another important question in future work is to understand how stimulation of more fine-grained subdivisions of the angular gyrus and posterior middle temporal gyrus differentially affects combinatorial semantic processes in language and vision (Seghier et al., 2010; Caspers et al., 2013; Seghier, 2013; Davey et al., 2015).

## **Studies of brain stimulation to temporoparietal brain regions**

Previous work has applied conventional anodal stimulation to left temporoparietal regions and shown improved word learning as well as improved word reading (Floel et al., 2008; Turkeltaub et al., 2012; Meinzer et al., 2014). In the current study, we found an effect on the semantic integration of words pairs. Even when both words in the pair were real words, matched on average single-word frequency, the stimulation effect was specific to those word pairs whose combinations were judged to be semantically meaningful. Therefore, we interpret the results in this study as unlikely to reflect only basic-level access to the individual words. Rather these effects appear to encompass higher-level processing of the word pair's associated meaning. Integrating semantic information is an integral aspect of both word learning and word reading, and thus it may be that improvements in the processes of semantic integration will be associated with faster word learning and word reading over time. It is also worth noting that the conventional tDCS used in the previous studies also affects relatively large regions of cortex, and stimulation to other temporal and parietal regions outside of the angular gyrus may lead to broader effects on the lexical-semantic network. Future work may be able to apply HD-tDCS to different regions of the left hemisphere network to identify differential contributions to word learning, word reading, and integrative semantic memory mechanisms in temporoparietal regions.

Recent studies using other brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) to study semantic processing and the angular gyrus have also shown this region to be causally involved in semantic memory tasks. When rTMS was used to target the angular gyrus to disrupt neural processing, it resulted in slowed reaction time on a semantic memory task but not on phonological or visual



letter-string discrimination tasks (Sliwinska et al., 2015). In a related study, Hartwigsen et al. (2015) examined coupled TMS perturbation of temporoparietal regions and IFG, and found semantic impairments when anterior IFG perturbation was coupled with rTMS to the left angular gyrus, but not when coupled with rTMS to the supramarginal gyrus. Hartwigsen et al. (2015a) also found that the degree of interference from rTMS to the left angular gyrus depended on the semantic predictability of sentences during comprehension.

Altogether, previous brain-stimulation studies have broadly implicated the angular gyrus in semantic processing. The findings in our current study build on this previous work and demonstrate for the first time a causal role for the angular gyrus in the process of semantic integration. Our findings also complement perturbation studies using rTMS by showing that excitatory stimulation from tDCS can be used to enhance semantic processing, motivating the study of tDCS as a potential therapy for patient populations with lexical-semantic impairments.

### **Item-wise effects from brain stimulation**

Many brain stimulation studies examine the effects of stimulation on categories of stimuli through random-effects analyses across participants. Here, we additionally examined the fine-grained effects of stimulation on individual stimuli. Using this approach, we were able to determine that the behavioral effects from stimulation were graded in relation to a continuous metric of semantic coherence. Of the meaningful word pairs, those that were less coherent at baseline gained the most from stimulation. It may be the case that stimulation to an associative region like the angular gyrus disproportionately facilitates the integration of weaker semantic associations. In contrast, word pairs that have strong

semantic associations at baseline are already easily integrated into coherent combinations and may exhibit ceiling effects when assessing performance gains from stimulation. Altogether, the findings from this item-analysis demonstrate the strong relationship between stimulation of the angular gyrus and measures of semantic coherence. When possible, it may benefit future studies to directly examine the relationship between brain-stimulation effects and specific item-level metrics for the phenomenon of interest.

### **Conclusions**

Our findings suggest that the angular gyrus plays an important role in the fluent composition of meaning in language. These results are consistent with the broader theoretical claim that the angular gyrus is a cortical semantic hub, characterized not only by the amodal nature of its representations but also by its specific role in high-level feature integration.

## CHAPTER 4

### Neural coding of fine-grained object knowledge in perirhinal cortex

Amy R. Price, Michael F. Bonner, Jonathan E. Peelle, and Murray Grossman (*in preparation as a brief-communications format*)

#### ABSTRACT

The ventral visual pathway transforms perceptual inputs into increasingly complex representations. Its highest stages are thought to contain abstract semantic codes that reflect statistical regularities learned over a lifetime of experience. Here we test this model by looking for evidence of a perceptual-to-conceptual transformation in the representation of visual objects. We used a novel stimulus set that allowed us to leverage the natural statistics of object color information to investigate semantic representations in the ventral visual stream, while controlling for shape information. We found that a region at the apex of this system—perirhinal cortex—encodes visual-feature combinations that are tuned to the statistics of the natural environment and underlie object meaning. Specifically, we found a double dissociation between the perceptual representation of color in V4 and a conceptual representation of color in perirhinal cortex, thus demonstrating a specific transformation from perceptual to conceptual object representations along the ventral visual stream. Altogether, these results suggest a mechanism in perirhinal cortex for transforming visual perceptual inputs into object representations that reflect long-term semantic knowledge.

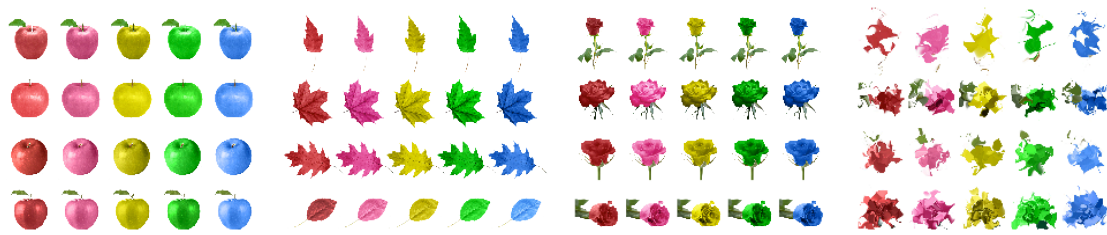
## INTRODUCTION

The ventral visual pathway transforms incoming information through a series of hierarchical stages known to be important for object form and identity (Felleman and Van Essen, 1991; DiCarlo et al., 2012; Kravitz et al., 2013). Along this pathway, neurons are tuned to increasingly complex properties of visual objects, and theories of object representation propose that abstract semantic information is encoded at the highest stages of this pathway. Much of the work examining high-level semantic aspects of object perception has focused on the representation of object categories. However, there is more to semantic representations of objects than their category labels. One essential aspect of the semantic system is the fine-grained information it contains about individual objects *within* a category. Within the category of leaves, for example, there are important semantic distinctions between green leaves, yellow leaves, and brown leaves. Thus an important and unanswered question is what regions of the ventral visual stream transform perceptual inputs into higher-level abstract codes that reflect the fine-grained semantic organization of objects within a category.

Here, we took advantage of the natural statistics of object color information to investigate semantic representations in the ventral visual stream. Many objects in our natural environment exist in a range of colors and exhibit clear statistical regularities. For example, we all know that roses are often red and violets are often blue. This information reflects the co-occurrence statistics of color and shape features in the natural environment, and it is a fundamental component of the abstract semantic knowledge that underlies our understanding of objects.

With this in mind, we developed a novel stimulus set that allowed us to dissociate lower-level perceptual codes from higher-level semantic knowledge. The stimuli were images of objects (i.e., apples, leaves, and roses) shown in five different colors (i.e., red, pink, yellow, green, and blue), as shown in Figure 11. Each color-and-shape combination was associated with a different semantic interpretation and defined the relationship of the object to other items within its category (e.g., green apples are semantically more similar to red apples but perceptually more similar to blue apples). Using this design, we were able to examine the perceptual representation of color in more posterior regions of the ventral visual stream (Figure 12A), while simultaneously testing for higher-level semantic representations that reflect abstract object knowledge in more anterior regions of this pathway (Figure 12B).

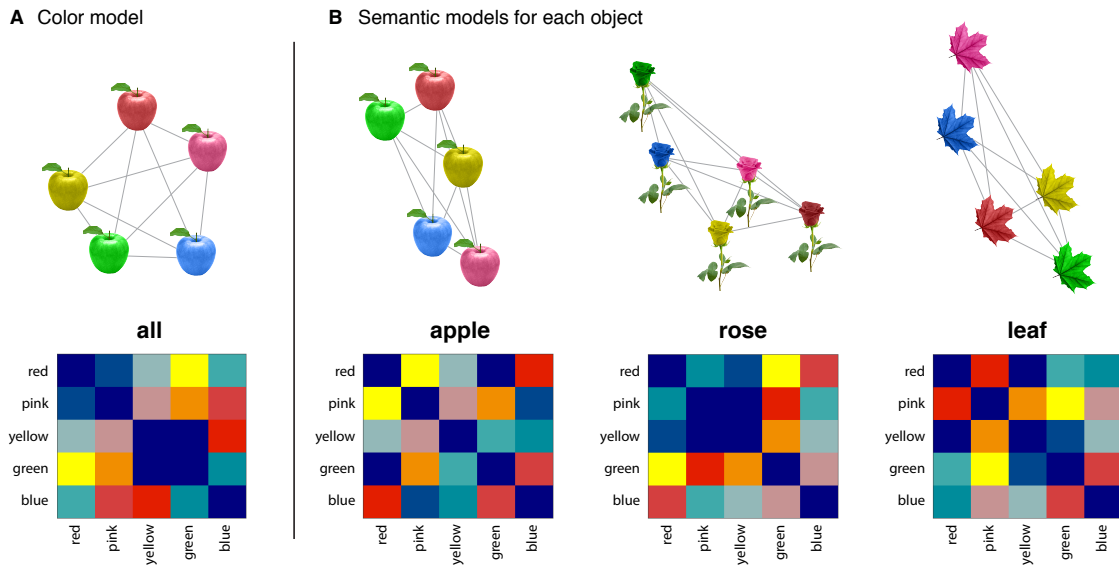
As expected, we found that V4, a region that has previously been shown to represent the perceptual properties of colors (Brouwer and Heeger, 2009, 2013), encoded these object stimuli in representational space that reflected their perceptual color similarity. In contrast to this, a more anterior region of this pathway, perirhinal cortex, encoded the exact same stimuli in a representational space that reflected the semantic similarity among colors of objects within a category. Indeed we observed a double dissociation between the perceptual coding of color in V4 and the semantic coding of color in perirhinal cortex. These results provide evidence of a transformation along the ventral visual stream from the perceptual representations of object features to their conceptual representations that reflects real-world knowledge of objects.



**Figure 11.** Five example stimuli from each object category in each color combination (A) roses (B) leaves (C) apples (D) non-object diffeomorphed images

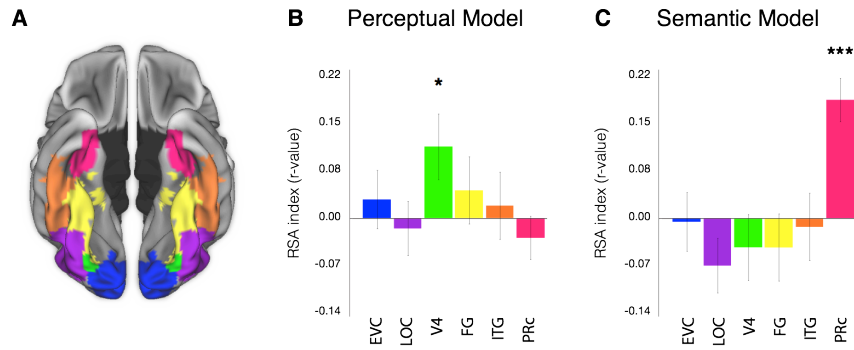
## RESULTS

We presented 810 unique object images to subjects while collecting fMRI data (stimulus duration = 1000 ms; interstimulus interval = 1500ms) from 15 categories of color and object combinations (Figure 11). In each region of interest (defined by anatomic and functional criteria; Materials) along the ventral visual stream (Figure 13A), we used representational similarity analysis to test for the coding of perceptual-color information (Fig. 12A) and semantic-color information (Fig. 12B).



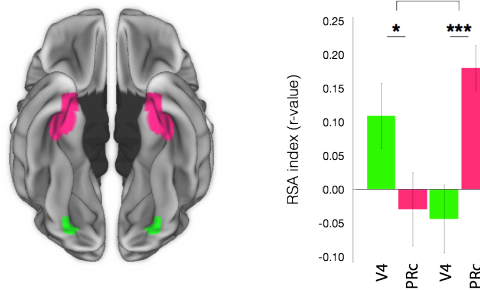
**Figure 12.** Models of representational dissimilarity for perceptual-color representations and category-specific semantic representations. Each plot shows a dissimilarity matrix and a two-dimensional embedding of stimuli for that model. (A) Perceptual-color model. This model is the same for all object categories. The apple category is shown as an example. (B) Semantic color models reflected category-specific co-occurrence statistics and thus differed across each object category.

Across all regions of interest, V4 was the only region to show a significant correlation with the color similarity model (Figure 13A;  $t = 2.22$ ,  $p = 0.02$ ; all other  $p$ -values  $> 0.13$ ). These results are consistent with the known role of V4 in color perceptual processing (McKeefry and Zeki, 1997; Brouwer and Heeger, 2009). Next, we tested for the semantic coding of object color information in the same set of ROIs. Across all regions of interest, perirhinal cortex, a region at the apex of the ventral visual stream, was the only region to show a significant correlation with the semantic models (Figure 13B;  $t = 5.41$ ,  $p < 0.001$ , all other  $p$ -values  $> 0.54$ ).



**Figure 13.** Representations of perceptual-color similarity and semantic-color similarity along the ventral visual stream. (A) Color-coded regions of interest. (B) Results for the perceptual-color model. The only region to show an effect for this model was V4 ( $p = 0.02$ ). (C) Results for the semantic model. The only region to show an effect for the semantic model was perirhinal cortex ( $p < 0.001$ ). EVC = early visual cortex, LOC = lateral occipital complex, FG = fusiform gyrus, ITG = inferior temporal gyrus, PRC = perirhinal cortex. \* $p < 0.05$ , \*\*\* $p < 0.001$

Transformation from perceptual to semantic color code



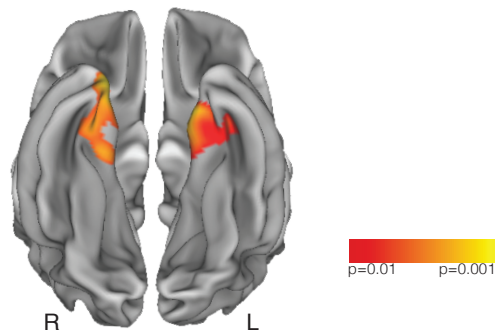
**Figure 14.** Double dissociation between the processing of color at a perceptual level in V4 and the processing of color at a semantic level in perirhinal cortex. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$



Furthermore, there was a significant interaction between color processing and semantic processing of color in V4 and perirhinal cortex (Figure 14; 2x2 repeated-measures ANOVA,  $F(1,15) = 14.89$ ,  $p = 0.002$ ). In direct comparisons, the color model had a significantly greater fit in V4 than in perirhinal cortex ( $t(15) = 2.13$ ,  $p = 0.025$ ), and the semantic model had a significantly greater fit in perirhinal cortex than in V4 ( $t(15) = 3.87$ ,  $p = 0.0008$ ).

To test for possible effects outside of our regions of interest, we performed a whole-brain searchlight analysis. There were no whole-brain corrected results. However at a lower uncorrected threshold ( $p < 0.001$  voxelwise), the only effects were in left and right perirhinal cortex (Figure 15).

Semantic searchlight analysis



**Figure 15.** Whole-brain searchlight analysis. Color scale ranges from  $p=0.01$  to  $p=0.001$  voxelwise (uncorrected).

## DISCUSSION

An important goal in the study of vision is to understand how online perception interacts with long-term semantic knowledge accrued over a lifetime of experience. For example, as observers of the world, we know that roses are typically red and violets are typically blue. But, as neurobiologists, we know little about how this statistical information is encoded in the visual system. Here, we showed that V4, a region known to process color information in the ventral visual stream, contains representations of the perceptual similarity space of object colors. In contrast, perirhinal cortex, a high-level region of the ventral visual stream, transforms these representations into a conceptual similarity space that reflects the statistical regularity of object colors and directly relates to the meaning of individual objects.

Previous work suggests that perirhinal cortex plays a critical role in representing highly specific objects and disambiguating visually similar objects (Buckley and Gaffan, 1998; Murray and Bussey, 1999; Bussey et al., 2002, 2003; Tyler, 2004; Devlin and Price, 2007). Our findings suggest a more complex mechanism for object representation in perirhinal cortex—specifically, that it not only disambiguates perceptually similar objects (e.g., red apple and pink apple) but also assigns similar representations to perceptually distinct objects with similar meanings (e.g., red apple and green apple). Thus perirhinal cortex appears to untangle the similarity space of lower-level perceptual inputs and organize individual objects according to their semantic interpretations.

## METHODS

*Participants.* Sixteen healthy subjects (7 female; mean age =  $24.6 \pm 2.6$  (s.d.)) with normal or corrected-to-normal vision were recruited from the University of Pennsylvania community. Participants provided written informed consent in compliance with procedures approved by the University of Pennsylvania Institutional Review Board.

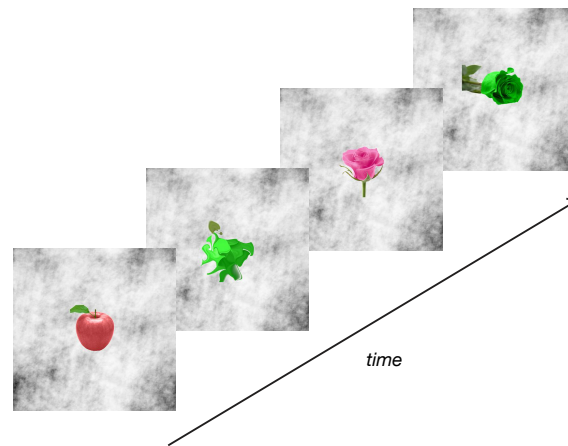
*MRI acquisition.* Participants were scanned on a Siemens 3.0 T Trio scanner. We acquired high-resolution T1-weighted structural images using an MPRAGE protocol (TR = 1620 ms, TE = 3.9 ms, flip angle =  $15^\circ$ , 1 mm slice thickness, 192 x 256 matrix, resolution = 0.9766 x 0.9766 x 1 mm). There were 3 functional scanning runs using (gradient echo echoplanar imaging sequences collecting 32 slices in descending order of 3 mm thickness, a between slice gap of 0.75 mm, and a resolution of 3 x 3 x 3mm). The field of view was 192 mm x 192 mm, matrix size of 64 x 64, flip angle of  $78^\circ$ , a TR of 2s, and a TE of 30ms. Each functional run lasted approximately 15 minutes.

*Stimuli.* Stimuli were colored objects presented on a phase-scrambled background. Three categories of objects (apples, leaves, and roses) were presented in five colors (red, pink, yellow, blue, and green). There was also a non-object condition that was presented in the same five colors. High-resolution images of natural objects were edited in Adobe Photoshop. The background was removed, leaving an object in isolation. The portion of the object containing the relevant color property was manually segmented and placed into a separate layer, where we were able to modify its color independent of the other object features (e.g., for an apple image, the body of the apple was segmented

and its color was modified without altering the stem or the leaves). This segmented portion of the object was first set to grayscale. We then created colored versions of each object by modifying the RGB color settings for this grayscale segmentation to red (RGB: 121 18 21), pink (RGB: 222 103 147), yellow (RGB: 187 174 30), blue (RGB: 0 67 166), and green (RGB: 0 171 0). Each object appeared in all five colors, ensuring that shape information was the same across all color conditions for a given object category. We repeated this procedure for 27 unique images within each object category (i.e., 27 apples, 27 leaves, and 27 roses). The same procedure and color settings were used for all objects. We also created mirror-flipped versions of the colored objects, resulting in 54 unique stimuli for each color-object condition (producing a total of 810 unique object stimuli). We created non-object images by applying a diffeomorphic warping procedure to the object stimuli described above. This procedure involves a smooth and continuous image transformation applied iteratively (40 iterations were used). The transformation preserves low-level perceptual properties of the stimuli while making them unrecognizable as real-world objects (Stojanoski and Cusack, 2014). All objects and non-object stimuli were centrally placed over a grayscale phase-scrambled background (the same background was used for all images).

*Stimulus presentation.* Stimuli were presented in an event-related design using a continuous carry-over sequence within each run (Aguirre, 2007). In each of the three runs, subjects viewed 270 unique object images (18 unique examples x 15 color-object conditions), as well as 36 unique non-object images. There were also 18 null events (5-s) in each run (null events were treated as an additional condition in our continuous carryover design). Each stimulus was presented on the screen for 1 s with an inter-trial

interval of 1.5 sec. On each trial subjects indicated by button press whether the image was an object or a non-object foil (Figure 16). Task accuracy was high. For object images the mean accuracy was 99.9% (SD = 0.1%), and for non-object images the mean accuracy was 96.4% (SD = 3.7%).



**Figure 16.** Visual object behavioral task. On each trial, participants viewed a single image on a phase-scrambled background and had to decide whether it was an object image or a warped non-object image.

*Regions of interest.* We defined a series of bilateral ROIs along the ventral visual pathway. These included ROIs for early visual cortex (EVC), V4, lateral occipital complex (LOC), inferior temporal gyrus (ITG), fusiform gyrus (FG), and perirhinal cortex. The ITG and FG ROIs were taken from the AAL atlas (Tzourio-Mazoyer et al., 2002). The EVC and LOC ROIs were taken from probabilistically defined parcels of functional localizer contrasts from a large number of subjects in a separate experiment (shared by Steven Marchette and described in (Marchette et al., 2014)). These parcels were created through an automated procedure that identifies clusters of common activation across individuals for a series of functional ROI contrasts (Julian et al., 2012). The LOC parcel was created from a contrast of objects>scrambled images, and the EVC parcel was created from a contrast of scrambled images>objects. We used the entire parcels for both EVC and LOC, and we did not apply any further voxel-selection procedures to these ROIs. Our V4 ROI was created by placing spheres with a 6-mm radius around MNI coordinates that were reported in a classic study of color-perceptual processing (McKeefry and Zeki, 1997), and which have previously been used to define ROIs for color perception (Coutanche and Thompson-Schill, 2015). The perirhinal cortex ROI was taken from a probabilistic map of anatomic segmentations (Holdstock et al., 2009) and was thresholded to include voxels with at least 30% overlap across subjects.

*fMRI preprocessing and modeling.* The fMRI data were processed and modeled using SPM12 (Wellcome Trust Centre for Neuro-imaging, London, UK) and MATLAB (R2014a Mathworks; The MathWorks, Natick, MA). For each participant, all functional images were realigned to the first image (Friston et al., 1995), co-registered to the structural

image (Ashburner and Friston, 1997), and normalized to standard Montreal Neurological Institute space (Ashburner and Friston, 2005). The images were spatially smoothed using a 3-mm FWHM isotropic Gaussian kernel. We modeled voxel responses to all conditions in each run in a single general linear model. Low-frequency drifts were removed using a high-pass filter with a cutoff period of 128 sec, and auto-correlations were modeled with a first-order autoregressive model. The parameter estimates for each condition were then averaged across runs. The resulting images were whole-brain maps of the voxel responses to each condition. We used these to characterize the information content in a series of ROIs through representational similarity analysis (Kriegeskorte and Kievit, 2013).

*Representational similarity analysis.* We used representational similarity analysis (RSA) to characterize the information encoded in the population responses of ROIs throughout the ventral visual pathway. For each ROI we constructed a neural dissimilarity matrix that represents all pairwise distances between conditions in a high-dimensional space defined by the ROI voxels. The voxel responses were z-scored across conditions. We computed dissimilarity as one minus the Pearson correlation coefficient between multivoxel response patterns. We also constructed dissimilarity matrices that represent the distances between conditions based on models of representational content. The specifics of these models are discussed below. We tested how well each model accounts for the representational structure in an ROI by calculating the Spearman correlation between the model and the neural dissimilarity matrices. The significance of each model was assessed using random-effects t-tests of the RSA correlations across subjects.

We examined two key models to test for coding of a perceptual color space and a semantic color space. The perceptual model was created from subjective evaluations of color similarity collected in a norming study (described below). This model reflects the perceptual similarity of the colors independent of the object categories, and it was thus the same for each object category (e.g., red is more similar to pink than to green). We converted these data into a dissimilarity matrix by taking the negative of the pairwise similarity values. The semantic model represents the dissimilarities between colors within each object category (e.g., red apple is more similar to green apple than to pink apple). These dissimilarities were calculated as the relative difference in semantic statistics (described below) using the absolute difference divided by the sum for each pairwise comparison. Because the semantic statistics were unique to each object category, these models differed across categories. Model fits were computed for each category separately, and we calculated the mean fit across categories. An important strength of this design is that we were able to calculate model fits within categories (i.e., apples, leaves, and roses), thus completely controlling shape information in both the perceptual and the semantic color models.

We also performed whole-brain searchlight analyses to test for possible effects outside of our regions of interests (Kriegeskorte et al., 2006). For this analysis, we performed the same RSA procedures described above using the multivoxel patterns within searchlight spheres (6-mm radius) centered at each voxel. RSA fits were written to the voxel at each searchlight's center, producing whole-brain maps of locally multivariate information coding. These images were smoothed with an isotropic Gaussian kernel (6-mm FWHM), and submitted to whole-brain voxelwise t-tests of random effects across subjects.



*Perceptual model.* We constructed a model of perceptual color similarity using subjective evaluations collected in a separate norming survey (N=18). This model captures color similarity independent of object categories. We presented the subjects with colored squares using the same RGB values used for the colored object images. Subjects judged the color similarity of the color swatches in a forced-choice two alternative task with an index swatch shown at the top and two choice swatches shown below. In an example trial, a subject might be shown a pink square at the top of the screen and asked to judge whether a red square or a blue square at the bottom of the screen is more similar. We constructed all possible pairings of index and choice sets (30 triads), resulting in an equal number of judgments for all pairwise comparisons of colors. We used these data to construct a similarity matrix. For each pairwise comparison in this matrix, we counted the number of times that subjects reported those two colors as similar across all trials of the similarity judgment task. In other words, we filled the cells of this matrix with frequency counts of similarity pairings. We then converted this into a dissimilarity matrix by taking the negative of the similarity values. The resulting matrix captures color relationships that are closely matched to the perceptual space of a color wheel, as can be seen in the two-dimensional embedding in Figure 12A.

*Semantic model.* We constructed a model of semantic color similarity based on the feature co-occurrence frequencies for the colors and object categories. This model reflects color similarity relationships that are unique to each object category (e.g., green apples are more similar to red apples than to blue apples based on how frequently apples occur in these colors). We used a metric of co-occurrence frequency that

captures the statistics of how people talk about object colors in written text. We reasoned that this metric would be strongly tied to how people think about and interpret these objects in the natural environment. We measured co-occurrence frequencies using Google ngram, a large corpus of English-language books (Michel et al., 2011). Specifically, we quantified the directional co-occurrence frequencies of the color and object terms using both the singular and plural forms of the object terms (e.g., “red apple” and “red apples”) from 2008 (the most recent available data). For all further analyses, we used log-transformed values of the co-occurrence statistics. To verify that these co-occurrence statistics related to the semantic interpretation of the objects, we asked the participants from the fMRI experiment to complete a series of subjective typicality ratings for the object images at the end of the study. The ratings were made on a 1-to-7 scale of highly atypical to highly typical. We were specifically interested in assessing whether subjects’ intuitions about color typicality related to the co-occurrence statistics of the object and color terms (e.g., that the high co-occurrence of “red apple” in text corresponded to subjective ratings that this color and object combination was highly typical). Indeed there was a strong correlation between the co-occurrence statistics and mean subjective ratings of typicality across all objects ( $r = 0.71$ ,  $p = 0.001$ ). These co-occurrence statistics were then used to construct a model dissimilarity matrix of the semantic color space for each object category. We calculated the relative difference in co-occurrence for all pairwise comparisons of objects within a category (i.e., the absolute difference divided by the sum of the co-occurrence statistics). These dissimilarity matrices capture a model in which highly typical colors for an object category are close together in representational space and atypical colors are farther away, as can be seen in the two-dimensional embedding in Figure 12B.

## CHAPTER 5

Advances in functional neuroimaging methods as well as intriguing patient data have allowed the field of semantic memory to build upon what philosophers of the 18th and 19th century could only surmise. Over the last 30 years, research on the biological principles of semantic memory has evolved to yield more fine-grained characterizations of the neuroanatomic correlates of the semantic memory system. This work has identified neural regions that appear to be specialized for specific categories of stored knowledge across varying levels of specificity (e.g., animate versus inanimate; insects versus mammals), and it has just begun to understand neural mechanisms for how this distributed information might interact. More recently, there has been a great deal of interest in understanding how heteromodal brain regions contribute to higher-level semantic memory functions, including combinatorial semantic processes. In this thesis, I aimed to advance our understanding of conceptual combination within the semantic memory system.

These studies were designed to address the following basic question: What brain regions support the ability to integrate our stored semantic knowledge? In the first three experiments, I examined simple two-word combinations and found consistent evidence that the left angular gyrus was functionally and causally involved in the process of lexical-semantic integration. These results are consistent with the known involvement of the angular gyrus in general lexical-semantic processing, but extend these findings to provide evidence of a specific integrative mechanism in lexical-semantic processing. These findings also provided the first causal evidence that the angular gyrus is necessary for combinatorial semantic processes. In the last experiment, I applied my

perspective on integrative processes in the semantic memory system to examine the issue of combinatorial codes in vision. This work sought to identify brain regions that encode knowledge of the feature combinations that define natural objects. Using a multivariate approach for analyzing representational codes in fMRI data, I identified representations in perirhinal cortex that track the meaning of object and color combinations. Perirhinal cortex is a subregion of the anterior temporal lobe that has previously been linked to object perception, high-level semantics, and cross-modal integration (Bussey et al., 2003; Tyler, 2004; Patterson et al., 2007; Holdstock et al., 2009; Mion et al., 2010; Clarke and Tyler, 2014). The findings from my study suggest that this region functions as a high-level hub at the apex of the ventral visual stream, where it encodes the semantic-feature combinations that support the representation of visual objects.

In the last few years, there have been a number of relevant neuroimaging publications on the topic of conceptual combination in language (also referred to as compositionality), as well as feature combination studies of object representation. These findings have been largely consistent with the results reported in this thesis, and they are discussed in detail in the next section.

### **Recent Work Related to Combinatorial Semantics**

In 2011, Pallier and colleagues published a study investigating constituent structure using sentences. They used a unique set of sentence stimuli that manipulated the size of linguistic constituents in each sentence using both real words and a set of jabberwocky words (i.e., pseudowords). The aim was to isolate neural regions where

activity increased parametrically with the number of meaningful words that were incorporated into the constituent structure of a sentence (critically, all sentences contained the same number of words: twelve). Using the jabberwocky sentence stimuli, they were able to examine the building of constituent “syntactic” structure inferred from grammatical morphemes modifying pronounceable pseudowords in the absence of semantic structure (i.e., in the absence of content words). Their analyses revealed three brain regions that increased in activity with the constituent size of content words but not jabberwocky words. These regions were the temporoparietal junction, the temporal pole, and anterior superior temporal sulcus. There were three regions that increased with constituent size regardless of whether the stimuli were content words or jabberwocky words. These regions were the left inferior frontal gyrus (both pars triangularis and pars orbitalis) and posterior superior temporal sulcus. These findings provide a nice dissociation between the representation of sentence-level semantic structure and of sentence-level syntactic structure. The coordinates for this temporoparietal region associated with semantic structure in this study border the region where I found a significant correlation for the building of higher-level meaning in adjective-noun combinations (note: the use of the term temporoparietal junction varies somewhat from study to study, but this region usually either borders or overlaps with the interior anterior portion of the angular gyrus depending on its exact placement).

At the end of 2010, Graves and colleagues published a study examining the neural basis of noun-noun combinations in which the stimuli were normed such that the same two words could be used in the forward and backward direction (e.g., lake house and house lake). In the forward direction, the stimuli formed meaningful combinations (e.g., flower girl) and in the reversed direction the stimuli formed minimally meaningful

combinations (e.g., girl flower). A contrast of the meaningful compared to the minimally meaningful noun-noun combinations revealed angular gyrus activation. These results are in line with the findings from my fMRI and patient findings in the angular gyrus, and they suggest that these results reflect a general semantic-integration mechanism regardless of the grammatical category of the modifier (i.e., noun-noun, as in Graves et al. 2010, or adjective-noun as in my work).

In 2013, Bemis and Pylkkanen published a set of magnetoencephalography (MEG) studies that examined the neural basis of simple conceptual combination using a set of two-word combinations (i.e., word compositions: “red boat”, “xkq boat”; word lists: “cup boat”, and “xkq boat”). There were two main regions where the activation profile showed an interaction between task (i.e., word composition versus word list) and number of words (i.e., one or two real words): the left angular gyrus and the left anterior temporal lobe. A similar effect was published by Bemis and Pylkkanen in 2011; however, in this case the analyses were restricted to regions of interest that were outside of the left angular gyrus.

In 2011, Schwartz and colleagues published findings that are relevant to both the lexical-semantic and visual-object studies from my thesis. In this paper, they reported a neuroanatomic dissociation between taxonomic and thematic knowledge in a large group of stroke patients. They examined semantic errors on an object-naming task and classified these errors as either taxonomic (e.g., seeing the object “apple” and naming it as a “pear” or a “grape”) or thematic (e.g., seeing the object “apple” and naming it as a “worm”, or seeing the animal “dog” and naming it as a “bone”). They found that lesions to the left anterior temporal lobe were associated with taxonomic production errors, whereas lesions to the temporoparietal region (encompassing the left angular gyrus)

were associated with thematic production errors. These results present a striking dissociation that lines up well with the findings from my fMRI studies. The findings from the visual-object study in Chapter 4 suggest that perirhinal cortex, a region of the anterior temporal lobe, encodes semantic representations of object-feature combinations. This leads to the prediction that lesions of perirhinal cortex would make high-level object representations less distinct and thus more confusable, which could produce the kind of semantic substitution errors observed by Schwartz and colleagues. Furthermore, Schwartz and colleagues found that the temporoparietal junction was associated with thematic substitutions, such as saying “worm” instead of “apple” (since worms are sometimes found in apples in nature). This type of knowledge requires high-level associations between the two concepts, and may be the type of information harnessed in a process like conceptual combination. To note, there is also a small degree of correlation in the angular gyrus for taxonomic errors in the study by Schwartz et al. (it does not reach significance, but it may not be statistically different from the taxonomic correlation in the anterior temporal lobe). It may be that both taxonomic and thematic knowledge rely on the left angular gyrus, but that high-level thematic information about how concepts interact (like worm to apple) is more vulnerable to disruption than taxonomic associations (like apple to grape).

In 2015, Coutanche and Thompson-Schill found that activity patterns in the left anterior temporal lobe were able to decode the identity of imagined objects at the same time that they were also able to decode color information about the objects in V4 and shape information in lateral occipital complex. These results are broadly consistent with the findings from the visual-object study in Chapter 4, although my findings point to a sub-region of the ATL that is more medial. Specifically, my results fall within perirhinal

cortex, a region that has previously been linked to object-specificity in both perception and memory (Bussey and Saksida, 2002; Bussey et al., 2003; Tyler, 2004; Clarke and Tyler, 2014). The results in Coutanche and Thompson-Schill span a more heterogeneous patch of tissue in mid-anterior temporal cortex that spans both lateral and medial structures. It may be that the object representations elicited by the mental imagery task in the Coutanche and Thompson-Schill study were more broadly distributed than the conceptual object representations examined in my study.

My studies have focused specifically on the semantic aspects of conceptual combination and on the neural regions implicated in these processes. However, there are many other interesting aspects to this complex process. For example, some research has demonstrated an abstract code for agent-patient relationships during sentence comprehension. Wu and colleagues (2007) demonstrated that patients with lesions affecting the lateral temporal cortex have impairments on interpreting agent-patient relationships in minimalistic picture diagrams (i.e., whom did what to whom). Building on this, Frankland and Greene (2015) found decoding of agent-patient information in the superior temporal cortex (e.g., predicting the agent of the sentence across many example verbs in which the noun was an agent, in both passive and active sentence forms). These results demonstrated an abstract code for agent-patient thematic roles that was not necessarily dependent on the semantic meaning of the constituents in the sentences.

Conceptual combination is a complex process that entails many different types of cognitive computations. This process allows us to form familiar combinations with ease on a daily basis (e.g., a red ball) but it also allows us to form novel combinations (e.g., a blue alligator). Furthermore, the meanings of combinations are dynamically altered



depending on the context (e.g., the phrase “she threw her hands up in the air” has different interpretations when preceded by “she was happy” or “she was angry”). In my experiments, I aimed to study the foundational components of the neural basis of conceptual combination in our semantic memory system, using well-controlled simplistic two-word adjective-noun combinations, before delving into the world of more complex combinations. In the next section, I discuss some of the differences between the lexical-semantic experiments and the visual object experiments, and what future directions might be taken to answer some of the open questions.

### **Future Directions**

One inherent difference between the lexical-semantic experiments and visual-object experiment is the modality of the stimuli. Both the angular gyrus and perirhinal cortex/anterior-parahippocampal cortex have been shown to represent amodal content when examining semantic categories of information (i.e., these regions have been shown to cross-classify between example pictures from the category fruit and example words from the category fruit) (Devereux et al., 2013; Fairhall and Caramazza, 2013). However, the angular gyrus has generally been more consistently implicated in the language literature than in the vision literature, and vice versa for the perirhinal cortex (with more reports of effects for visual stimuli than for lexical stimuli). The degree to which each of these regions represents amodal combinatorial codes for both words and objects is still an open question.

Another key difference between these two studies is the level at which the knowledge is represented. For example, viewing the visual object “red apple” involves

representing a specific instantiation of a red apple in the world, whereas reading the word pair “red apple” involves a representation with much greater generalization across a wide array of what could be considered a “red apple.” Indeed, there is evidence that regions within the anterior temporal lobes are associated with representing specific and unique instances within a category (Kriegeskorte et al., 2007; Ross et al., 2010; Bi et al., 2011; Abel et al., 2015). It may be that a region like the angular gyrus underlies higher-order generalizations that are necessary for abstract thought, but that regions within the anterior temporal lobe represent specific and unique instances of objects, people, and other entities.

In order to address these outstanding questions, I have a follow-up experiment that is designed to determine whether there are overlapping amodal combinatorial codes between the lexical modality and visual modality in semantic memory. In the subjects who participated in the visual-object study described in Chapter 4, I also collected fMRI data while they viewed word pairs that corresponded to the object stimuli in the first part of the study (e.g., “red apple”, “green apple”). This additional two-word combinatorial data set will allow us to directly examine the extent to which combinatorial codes in language correspond to the same visual-feature combinations in object perception.

This follow-up data set also addresses another key difference between the fMRI study of lexical semantics and the fMRI study of visual-object semantics, which is the analytic approach. In the study of lexical-semantic combinations, I was examining univariate signals that corresponded to the meaningfulness of the two-word combinations. In contrast, for the visual-object study I learned to implement a multivariate analytic approach that allowed me to test more fine-grained questions about the nature of combinatorial representations in vision. This multivariate approach opens

up many avenues for future exploration into the functional organization of semantic combinations in the brain. In the follow-up data set described above, I applied color modifiers to the nouns (e.g., red leaf, green leaf). But this could be expanded to examine other feature-based conceptual combinations formed from various categories of modifiers (e.g., colors, sizes, shapes, textures) and various categories of entities (e.g., mammals, insects, fruits, vegetables, tools). Using multivariate analyses, I may be able to examine more complex aspects of lexical-semantic integration. For example, I would predict that multivariate fMRI codes distinguish between combinations with emergent features and those that can be more simply characterized as weighted-feature combinations. This type of approach holds promise for revealing neural regions that underlie a broad range of combinatorial codes in both language and vision.

### **Concluding Thoughts**

In all of the research presented in this thesis, I aimed to use minimalistic stimuli in order to examine the fundamental neural mechanisms for combinatorial semantics. In the lexical-semantic study, I used simple two-word combinations (e.g., loud car, plaid jacket). In the visual object study, I used the same exact visual-object shapes and only modified their color combinations. I interpret these results as providing well-controlled evidence that even simple combinatorial changes are fundamental to the representational codes in heteromodal regions in the semantic system. I think that the basic mechanisms and ideas gained from this work provide a motivation and conceptual framework for how to answer more complex issues on combinatorial semantics in future

work. I plan to extend this line of work to more complex lexical stimuli (e.g., sentences, narratives) and more complex visual stimuli (e.g., scene and object interactions during visual perception), to be able to answer similar kinds of questions about the semantic memory system in a setting that is more naturalistic and representative to our everyday experience.

Altogether this work identifies two key regions implicated in the representation of combinatorial information in semantic memory. These findings contribute to our understanding of how heteromodal brain regions in our semantic memory system contribute to the fundamental process of integrating information into higher-level conceptual codes.

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