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Neuropsychological evidence for the functional role of the uncinate fasciculus in semantic control

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ABSTRACT

Understanding a word requires mapping sounds to a word-form and then identifying its correct meaning, which in some cases necessitates the recruitment of cognitive control processes to direct the activation of semantic knowledge in a task appropriate manner (i.e., semantic control). Neuroimaging and neuropsychological studies identify a fronto-temporal network important for word comprehension. However, little is known about the connectional architecture subserving controlled retrieval and selection of semantic knowledge during word comprehension. We used diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging (rs-fMRI) in aphasic individuals with varying degrees of word comprehension deficits to examine the role of three white matter pathways within this network: the uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF), and inferior fronto-occipital fasciculus (IFOF). Neuroimaging data from a group of age-matched controls were also collected in order to establish that the patient group had decreased structural and functional connectivity profiles. We obtained behavioral data from aphasic participants on two measures of single word comprehension that involve semantic control, and assessed pathway functional significance by correlating patients' performance with indices of pathway structural integrity and the functional connectivity profiles of regions they connect. Both the structural integrity of the UF and the functional connectivity strength of regions it connects predicted patients' performance. This result suggests the semantic control impairment in word comprehension resulted from poor neural communication between regions the UF connects. Inspections of other subcortical and cortical structures revealed no relationship with patients' performance. We conclude that the UF mediates semantic control during word comprehension by connecting regions specialized for cognitive control with those storing word meanings. These findings also support a relationship between structural and functional connectivity measures, as the rs-fMRI results provide converging evidence with those obtained using DTI.

1. Introduction

Understanding a word, consciously a fast and easy process, requires a number of computational stages including matching a word's sound input with its arbitrary word form in order to identify its meaning (Hillis, Rapp, Romani, & Caramazza, 1990; Shelton & Caramazza, 1999) and cognitive control processes to regulate the activation of semantic knowledge (semantic control; e.g., Jefferies & Lambon Ralph, 2006). Language comprehension recruits a number of disparate brain regions in the left frontal and temporal cortices (e.g., Fedorenko, Hsieh, Nieto-Castanon, Whitfield-Gabrieli, & Kanwisher, 2010), that when damaged due to stroke results in varying degrees of comprehension impairments (e.g., Dronkers, Wilkins, van Valin, Redfern, & Jaeger, 2004). However, lesion location does not always coincide with specific language deficits (Dronkers, Redfern, & Ludy, 1995; Fridriksson, Bonilha, & Rorden, 2007; Price, Seghier, & Leff, 2010), which complicates the neuroanatomical localization of language comprehension. An increasingly popular hypothesis proposes that aphasic speakers' deficits arise from impairments in semantic control (e.g., Jefferies & Lambon Ralph, 2006), suggesting that regions implicated in cognitive control fail to interact effectively

Abbreviations: ATL, Anterior temporal lobe; AWPV, Auditory word-picture verification task; BOLD, Blood oxygenation level dependent; BORB, Birmingham object recognition battery; DTI, Diffusion tensor imaging; FA, Fractional anisotropy; IFOF, Inferior fronto-occipital fasciculus; ILF, Inferior longitudinal fasciculus; LIFG, Left inferior frontal gyrus; LIFGorb, Left inferior frontal gyrus pars orbitalis; MidAntTemp, Middle-anterior temporal lobe; MidPostTemp, Middle-posterior temporal lobe; PostLIFG, Posterior left inferior frontal gyrus; PostTemp, Posterior temporal lobe; PPT, Pyramids and palm trees test; rs-fMRI, Resting-state functional magnetic resonance imaging; UF, Uncinate fasciculus; WAB, Western aphasia battery

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with semantic knowledge stored elsewhere. While research identifies subcortical structures interconnecting regions critical for language comprehension (Turken & Dronkers, 2011), the behavioral roles of these white matter pathways are not well understood. Thus, the goal of this research was to classify the neural substrates of semantic control during word comprehension by investigating the behavioral significance of structural and functional connections in aphasic speakers who have damage to the fronto-temporal language network.

Evidence for a dissociation between semantic representations and control processes involved in language comprehension primarily comes from comparisons between word comprehension deficits in patients with the semantic variant of primary progressive aphasia (i.e., semantic dementia) and aphasia due to stroke (Jefferies & Lambon Ralph, 2006; Jefferies, Patterson, & Lambon Ralph, 2008; Corbett, Jefferies, Ehsan, & Lambon Ralph, 2009a). Both patient groups perform poorly on tests of semantic memory. However, patients with semantic dementia show item consistency across varying task demands, yet those with aphasia perform consistently only when the tasks demands are consistent (e.g., picture and word versions of the Camel and Cactus Test (CCT); Jefferies & Lambon Ralph, 2006). Thus it is argued, although the level of comprehension impairment appears similar in the two groups (e.g., Jefferies & Lambon Ralph, 2006), patients with semantic dementia demonstrate poor word comprehension due to a gradual loss of semantic representations (Warrington, 1975; Davies et al., 2005), whereas aphasic speakers' difficulties with word comprehension are argued to typically arise from a failure to control the activation of stored semantic knowledge (i.e., semantic control; Corbett, Jefferies, & Lambon Ralph, 2009b; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010).

In the context of word comprehension, semantic control refers to the recruitment of cognitive control mechanisms in order to direct semantic activation towards the relevant word meaning (retrieval) and to select that meaning from amongst related competing meanings (selection). Controlled retrieval processes are necessary when bottom-up, or stimulus-driven cues provide insufficient activation of semantic knowledge to determine the target response, or when automatic activation of task relevant information does not occur, whereas controlled selection occurs after retrieval in cases where active representations related to the target compete for selection (reviewed in Badre and Wagner (2007)). Consistent with this account, aphasic individuals have difficulty retrieving the meaning of a target word when the cue and target are weakly related, and their performance is also impaired when the task requires selecting a response in the face of semantic competitors (e.g., Jefferies & Lambon Ralph, 2006). Thus, in some cases, word comprehension requires semantic control processes for retrieving and selecting the most relevant representations from stored semantic knowledge corresponding to the task demands (Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2012). Taken together, these findings suggest dissociable processes in word comprehension, where the control over semantic knowledge can be separately impaired from the store of semantic knowledge.

The dissociation between deficits of storing vs. controlling the activation of semantic knowledge in semantic dementia and stroke aphasic patients is associated with different patterns of brain damage. Typically, semantic dementia patients have atrophy of the anterior temporal lobes (ATL), where the extent of ATL atrophy relates to the level of comprehension impairment (e.g., Mummery et al., 2000). In contrast, ATL damage rarely occurs due to stroke (e.g., Caviness et al., 2002), and comprehension impaired stroke patients tend to have damage to the prefrontal and/or temporo-parietal regions within the left hemisphere (e.g., Jefferies & Lambon Ralph, 2006). Convergent findings from neuroimaging studies of healthy participants indicate that language comprehension not only involves a system storing semantic knowledge underpinned by the ATL (Lambon Ralph, Pobric, & Jefferies, 2009; Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Visser, Jefferies, & Lambon Ralph, 2010; de Zubicaray, Rose, & McMahon, 2011), but it also involves modulation from cognitive control mechanisms thought to be associated with the left inferior frontal gyrus (LIFG; Thompson-Schill, Bedny, & Goldberg, 2005; Bedny, McGill, & Thompson-Schill, 2008; Novick, Trueswell, & Thompson-Schill, 2010), which is argued to support the retrieval and/or selection of semantic and other types of knowledge (see Badre & Wagner, 2007; Snyder, Banich, & Munakata, 2011).

However, the role of the temporo-parietal cortex in controlling the activation of semantic knowledge is less clear. Neuroimaging studies of healthy participants suggest that word comprehension tasks requiring semantic control equally recruit the LIFG and posterior temporal cortex (Whitney, Jefferies, & Kircher, 2011a) and the temporary disruption of the function of either site with repetitive transcranial magnetic stimulation affects semantic control performance on tasks tapping controlled retrieval and selection during comprehension (Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011b; Whitney et al., 2012). In contrast, other results indicate that the role of posterior temporal regions in semantic control processes differs from that of the LIFG (e.g., Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005). Importantly, patients with prefrontal damage manifest greater semantic control deficits than those found in patients with damage restricted to the temporo-parietal cortex (Gardner et al., 2012). Thus, the precise role of posterior temporo-parietal regions in semantic control remains to be disambiguated. Given the distinction between regions specialized for storing semantic knowledge and those hypothesized to support cognitive control of semantic knowledge, this suggests that white matter pathways interconnecting these regions should be critical for semantic control processes, and the investigation of their functional significance should add to our current understanding of the neural correlates mediating semantic control during word comprehension.

Recent diffusion tensor imaging (DTI) studies identify at least three ventral fiber tracts connecting regions hypothesized to be important for semantic control processes. However, the precise functional role of each pathway remains to be clarified. Ventral white matter tracts include the uncinate fasciculus (UF), the inferior longitudinal fasciculus (ILF), and the inferior fronto-occipital fasciculus (IFOF). Both the UF and the ILF terminate in the ATL, where the former projects to the inferior frontal lobe and the latter projects to the posterior temporal cortex. The IFOF connects the posterior temporal cortex with the inferior frontal lobe (Catani & Thiebaut de Schotten, 2008). On the basis of their anatomical projections, the UF and ILF can be hypothesized to support aspects of semantic control, as they connect the semantic knowledge store with regions implicated in control processes. Evidence consistent with this function of the UF was obtained in a study of healthy participants identifying this tract as connecting anterior temporal and prefrontal cortices simultaneously active during a homonym meaning decision-making task, where indices of structural and functional connectivity patterns predicted performance (Duda, McMillan, Grossman, & Gee, 2010). Although the ILF connects posterior regions proposed to support control processes, recent DTI studies of healthy participants show that the ILF also connects regions more active for meaningful speech compared with pseudospeech (Saur et al., 2008, 2010), and the integrity of this pathway predicts performance on a sound-to-word learning paradigm (Wong, Chandrasekaran, Garibaldi, & Wong, 2011). Thus in contrast to the UF, the ILF may instead