



Altered brain response for semantic knowledge in Alzheimer's disease

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ABSTRACT

Word retrieval deficits are common in Alzheimer's disease (AD) and are thought to reflect a degradation of semantic memory. Yet, the nature of semantic deterioration in AD and the underlying neural correlates of these semantic memory changes remain largely unknown. We examined the semantic memory impairment in AD by investigating the neural correlates of category knowledge (e.g., living vs. nonliving) and featural processing (global vs. local visual information). During event-related fMRI, 10 adults diagnosed with mild AD and 22 cognitively normal (CN) older adults named aloud items from three categories for which processing of specific visual features has previously been dissociated from categorical features. Results showed widespread group differences in the categorical representation of semantic knowledge in several language-related brain areas. For example, the right inferior frontal gyrus showed selective brain response for nonliving items in the CN group but living items in the AD group. Additionally, the AD group showed increased brain response for word retrieval irrespective of category in Broca's homologue in the right hemisphere and rostral cingulate cortex bilaterally, which suggests greater recruitment of frontally mediated neural compensatory mechanisms in the face of semantic alteration.

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1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by neuronal atrophy, synapse loss, and the abnormal accumulation of neuritic plaques and neurofibrillary tangles. In the usual case, AD neuropathology initially involves medial temporal lobe structures (e.g., hippocampus and entorhinal cortex) and then extends to temporal, parietal, and frontal lobe association cortices as the disease progresses (Braak & Braak, 1991; Brewer & Moghekar, 2002). These neuropathological changes cause significant cognitive and behavioral disturbances that characterize the global AD dementia syndrome (Salmon & Bondi, 2009). Although the most prominent feature of this dementia syndrome is a profound amnesia (e.g., episodic memory loss), language dysfunction in the form of word finding difficulties is also an early and ubiquitous aspect of the disease (Salmon, Butters, & Chan, 1999). In

fact, some studies suggest that word-finding ability and other manifestations of semantic knowledge deteriorate as much as episodic memory and more than executive function during the prodromal phase of AD (Mickes et al., 2007).

The language dysfunction associated with AD is evident on tests of confrontation naming, verbal fluency, and semantic categorization (Bayles, Tomoeda, & Trosset, 1990; Chan, Salmon, Nordin, Murphy, & Razani, 1998; Hodges & Patterson, 1995; Monsch et al., 1992; Nebes, 1989; Salmon, Heindel, & Lange, 1999). Considerable evidence suggests that patients' performance on these tests is indicative of a deterioration of semantic knowledge rather than simply an impaired ability to retrieve lexical information from intact semantic stores (Astell & Harley, 1996; Barbarotto, Capitani, Jori, Laiacona, & Molinari, 1998; Bayles, Tomoeda, & Cruz, 1999; Nakamura, Nakanishi, Hamanaka, Nakaaki, & Yoshida, 2000; Paganelli, Vigliocco, Vinson, Siri, & Cappa, 2003). Consistent with a degradation of semantic knowledge, AD patients tend to make highly consistent errors for the same concept (e.g., miss the same items) across test modalities and methods of access (Chertkow & Bub, 1990; Hodges, Salmon, & Butters, 1992; Norton, Bondi, Salmon, & Goodglass, 1997; Salmon, Butters, et al., 1999), they are more impaired (relative to healthy control subjects) on seman-

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tically demanding category fluency tasks than on letter fluency tasks (Butters, Granholm, Salmon, Grant, & Wolfe, 1987; Monsch et al., 1992), and they make an abnormally high proportion of semantically related errors on confrontation naming tests with a propensity to generate the more general superordinate category name (e.g., “an animal”) rather than the specific item name (e.g., “a camel”) (Barbarotto et al., 1998; Hodges, Salmon, & Butters, 1991). These results do not, however, preclude the possibility that AD also impairs the ability to access lexical representations from the semantic store (e.g., Nebes, Martin, & Horn, 1984). Indeed, patients with AD exhibit semantic priming effects under some conditions (Nebes & Brady, 1990) and their semantic memory deficits are more salient when retrieval is difficult (Hodges et al., 1992). Furthermore, AD patients are particularly impaired in producing low-frequency picture names which is consistent with a post-semantic processing deficit since frequency effects are thought to arise during phonological retrieval (Gollan, Salmon, & Paxton, 2006). Thus, the semantic memory impairment exhibited by patients with AD may reflect both a degradation of semantic knowledge and inefficient retrieval.

Although the observation of semantic memory deterioration in AD is well established, its nature is actively debated. A major point of debate is whether the semantic memory deficit in AD reflects loss of specific knowledge of particular concepts, or loss of distributed knowledge of features and attributes (e.g., physical features and function) (Alathari, Trinh Ngo, & Dopkins, 2004; Done & Hajilou, 2005; Harley & Grant, 2004). Support for the claim that specific concepts are lost comes from category-specific effects such as findings that some AD patients perform worse on language tasks that require knowledge of living things versus those that require knowledge of nonliving things (Chan, Salmon, & De La Pena, 2001; Chertkow & Bub, 1990; Garrard, Patterson, Watson, & Hodges, 1998; Silveri, Daniele, Giustolisi, & Gainotti, 1991; Zannino, Perri, Carlesimo, Pasqualetti, & Caltagirone, 2002), whereas other AD patients show the opposite pattern of category-specific deficits, with worse performance on artifacts compared to biological items (Gonnerman, Andersen, Devlin, Kempler, & Seidenberg, 1997). However, the results of several studies, including a recent meta-analysis (Laws, Adlington, Gale, Moreno-Martinez, & Sartori, 2007), suggest that category-specific deficits in AD may be artifactual and actually reflect differences in the degree of featural information (e.g., size and function) needed to identify exemplars in various categories. Evidence of decline in featural knowledge in AD comes from reports that patients show selective difficulties in identifying specific features or properties of objects (Chan, Butters, Salmon, & McGuire, 1993; Sacchett & Humphreys, 1992) and are less consistent than nondemented elderly in their use of features when classifying exemplars into categories (e.g., predation, domesticity, and size for the category “animals”) (Chan, Butters, & Salmon, 1997).

The resolution of this debate is complicated by the ongoing controversy regarding the organization of semantic knowledge in the healthy brain. Briefly, theoretical accounts of category-specific effects differ primarily as to whether they view semantic knowledge as (1) modularly represented in a unitary semantic system (Caramazza & Shelton, 1998; Rogers et al., 2004) or (2) distributed across many attribute-specific subsystems (e.g., visual, sensorimotor and functional) that differ in degree of categorical organization (Coltheart, Inglis, Cupples, Michie, & Budd, 1998; Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Humphreys & Forde, 2001; Moss & Tyler, 2000; Sartori & Lombardi, 2004; Stewart, Parkin, & Hunkin, 1992; Zannino, Perri, Pasqualetti, Caltagirone, & Carlesimo, 2006). While these parallel distributed processing (PDP) models may disagree on whether or not there is a unitary semantic system, they tend to agree that concepts emerge from patterns of activation across sets of distributed features (Aronoff et al., 2006; McRae, de Sa, & Seidenberg, 1997; Shallice, 1988). According to one seminal PDP neural network model of semantic

processing put forth by Rogers and colleagues, semantic knowledge arises from the interactive activation of modality-specific representations of objects that are distributed throughout the cortex and converge in a cross-modal ‘hub’. These units are thought to receive input directly from the environment and represent anatomically distinct regions of cortex that subserve a particular function (e.g., visual information) (Lambon Ralph, Lowe, & Rogers, 2007; Rogers et al., 2004). Because concepts within a given category may have more overlapping features than concepts from another category, damage affecting feature knowledge may result in apparent category-specific deficits. In other words, since living things rely more heavily on perceptual features and nonliving things rely more heavily on functional features (Farah & McClelland, 1991; Warrington & McCarthy, 1987), according to computational models, differential category-specific impairments for either living or nonliving items may emerge from widespread damage to distributed features (as in AD) if the features are intercorrelated (e.g., activated simultaneously for many items within a category) or distinguishing (e.g., occurs almost exclusively for one item within a category to differentiate it from related ones) (Gonnerman et al., 1997).

Regardless of whether category-specific deficits are caused by damage to conceptual representations in specialized brain regions or damage to distributed representations within nonspecialized brain areas (Aronoff et al., 2006; Zahn et al., 2006), they appear to emerge from localized changes in neural function that can be detected using fMRI (Thompson-Schill, 2003). Many functional neuroimaging studies in healthy adults suggest that there are localizable regions specialized for processing category and feature knowledge. The fusiform gyrus, for example, is a focal point for the convergence and integration of visual semantic information, and evidence indicates a reliable difference along its medial/lateral dimension for the categorical distinction between nonliving and living things (Chao, Haxby, & Martin, 1999; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999; Weisberg, van Turenhout, & Martin, 2007; Whatmough, Chertkow, Murtha, & Hanratty, 2002; Wierenga et al., 2009). Furthermore, we recently reported a dissociation between category (living vs. nonliving) and attribute (global vs. local form) knowledge in the fusiform gyrus of healthy younger and older adults (Wierenga et al., 2009).

A number of additional studies using fMRI in healthy adults have shown localized function related to various aspects of processing semantic knowledge. For example, studies indicate that the lateral frontal cortex of the language dominant hemisphere (i.e., Broca’s area, cortex along the inferior frontal sulcus, and possibly pars orbitalis) is involved in selection, retrieval and execution of lexical-semantic responses (Barch, Braver, Sabb, & Noll, 2000; Crosson et al., 1999; Damasio & Anderson, 1993; Gabrieli, Poldrack, & Desmond, 1998; MacDonald, Cohen, Stenger, & Carter, 2000; Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). Medial frontal lobe cortical regions, especially those at the border of the pre-supplementary motor area (SMA) and the rostral cingulate zone, are involved in initiation of language, cognitive control, and monitoring conflict between competing responses (Barch et al., 2000; Carter et al., 2000; Crosson et al., 1999; Damasio & Anderson, 1993). The results of these studies suggest that the left prefrontal cortex as well as bilateral ventral temporal cortex may be involved in a “general-purpose” semantic system for the respective retrieval or storage of semantic knowledge (Thompson-Schill, 2003).

Relatively few studies have examined the effects of AD on the neural substrates of semantic memory. Zahn et al. (2006) reported that left posterior fusiform gyrus hypometabolism was correlated with impaired knowledge of visual properties of living objects in patients with AD, whereas hypometabolism in the left anterior temporal region was correlated with impaired knowledge of visual and

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