

Language Processing in Dementia

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The traditional view of dementia is that patients experience a global decline in cognition and that there is nothing particularly unique about language. This sharply contrasts with the classic position that aphasia following stroke reflects focal damage to “language-specific” processing centers in the brain (Broca, 1863; Wernicke, 1874). We argue that there is indeed something special about language processing in dementia and that specific linguistic processes are compromised. Moreover, components of language that demand executive resources such as working memory and inhibitory control are particularly vulnerable to these conditions. Here we focus our discussion on the interaction of resource-related deficits with language-specific impairment incurred in two dementia subpopulations: Alzheimer’s disease (AD) and frontotemporal dementia (FTD).

Some Components of Language

Language is the uniquely human capacity that can represent concepts through an arbitrary set of acoustic symbols (☼ = “sun”) and allows us to combine these symbols in a rule-governed manner, thus yielding a system of limitless generativity (Pinker & Jackendoff, 2005). Language is sufficiently flexible to reference concrete concepts (e.g., There is a dog.), as well as temporally remote events and abstract propositions (e.g., She told the truth last week). Language production and comprehension are supported by highly interactive cognitive processes. We begin by discussing key components of language followed by the neurological basis for linguistic degradation in AD and FTD.

Phonology

In most spoken languages concepts are represented by words, and words are composed of smaller units of sound called *phonemes*. Phonemes are acquired early in life and have language-specific acoustic properties. For example, *lap* and *rap* sound and mean different things to a monolingual English speaker, whereas native speakers of Japanese have difficulties perceiving this sound difference (Abramson & Lisker, 1970). Similarly, native English speakers have difficulties perceiving tonal markers of Mandarin Chinese. In addition to phonology, words are represented in written form via orthography. The orthographic system of English grossly approximates its phonological system. Yet, this sound–letter correspondence is imperfect (e.g., yacht, colonel).

Many psycholinguistic theories assume that the phonological and orthographic forms of words are stored in human memory as whole units. That is, concepts have corresponding auditory and visual word forms (i.e., lexical representations) that exist independent of their meaning (Coltheart, 2004). Lexical and phonological deficits such as acquired dyslexia and pure word deafness significantly impact language perception. Impairment within phonological and orthographic domains occurs in both AD (Biassou et al., 1995; Croot et al., 2000; Weiner et al., 2008) and FTD (Ash et al., in press; Gorno-Tempini et al., 2006; Kwok et al., 2006). We review these deficits in the respective sections to follow.

Semantics/Word meaning

Assuming intact phonology, language comprehension also demands access to one's stored conceptual knowledge via *semantic memory*. During the past two decades, our understanding of the structure of semantic memory has vastly progressed as a result of neuroimaging and patient-based studies. Both lines of research have demonstrated that temporal lobe structures are critical for knowledge representation. For example, whether one hears the word *dog* or sees a picture of a dog, shared areas of temporal cortex are active in relation to the concept, DOG. Common areas of activation include ventral temporal cortex (e.g., fusiform gyrus), anterolateral temporal cortex, and the posterior middle temporal gyrus (Bright et al., 2004; Thierry & Price, 2006). These cortical regions are prominently affected in both FTD and AD (Bonner et al., 2009; Galton et al., 2001; Mesulam et al., 2003; Patterson, Nestor et al., 2007; Rosen et al., 2002; Yi et al., 2007). We review semantic memory impairment as the second major component that affects language in dementia.

Naming

Naming engages a large-scale neural network dedicated to phonological, lexical, and semantic levels of processing. Neural structures that support the various

components of naming are susceptible to different types of brain damage. It is well established that naming impairment (i.e., anomia) is among the most common diagnostic features of stroke aphasia. However, anomia has also been identified as among the most common and socially isolating aspects of dementia (Bayles & Kim, 2003; Graham et al., 2001; Grossman et al., 2004). We review naming as the third major aspect of language processing in dementia.

Syntax

Language competency demands far more than the simple concatenation of single words. Language is structured via grammar, a rule-governed system for combining individual elements of language. Agrammatism, a neurogenic language deficit that affects grammar, is characterized by diminished syntactic complexity with elimination of function words (e.g., the) and bound morphemes (e.g., -ing). There is also a concurrent reduction in phrase length (e.g., John go store) and simplification of long-distance syntactic relationships between words in a sentence. Agrammatism also affects comprehension of noncanonical sentence structures such as passives (e.g., Mary was kissed by Jane). Neuroimaging and lesion studies have long implicated inferior frontal lobe structures in grammatical processing (Friederici, 2001). Grammatical deficits have been reported in both AD (Grober & Bang, 1995) and the non-fluent variant of primary progressive aphasia (Ash et al., 2009; Peelle et al., 2008; Peelle, Cooke et al., 2007). Syntax is the fourth major component of language processing in dementia we will address here.

Narrative discourse

Narrative discourse is a resource-demanding process that is critical for human communication. “How was your day?” is an invitation for a narrative, and in order to effectively frame a response, one must accurately sequence events, convey meaningful content, and maintain a cohesive thread throughout the story. These processes tax executive resources necessary for planning, as well as episodic and working memory resources necessary to retrieve remote events. Due to the multiplicity of these demands, perhaps it is not surprising that patients have difficulties with discourse production (Ash et al., 2006; Cosentino et al., 2006). We address the integrity of narrative discourse as the final aspect of language processing in dementia.

Dementia

Dementia is perhaps most commonly associated with an impairment of episodic memory. Although this is true of AD, this particular disease also includes among

its criteria a disorder of language, entailing difficulty with naming or comprehension. In addition, while AD is the most common neurodegenerative condition, there is another large group of dementias that is characterized by their generally earlier age of onset. These conditions include FTD, corticobasal degeneration (CBD), Parkinson's disease, motor neuron disease, and others. Although any one of these conditions is less common than AD, they are collectively almost as common as AD in the population of patients with dementia that are younger than 65 years of age. Common symptoms of these dementias include a social disorder involving personality change, impulsivity, agitation, visuospatial difficulty, and impaired problem solving, or primary progressive aphasia (NINDS, 2009). The hallmark of a dementia, from this perspective, is progressive decline in *any* cognitive or social domain after an adult level of competence has been acquired. Here we focus on language comprehension and production in two of the best-characterized dementias: AD and FTD.

Alzheimer's Disease

AD is the most common form of dementia in the United States, affecting an estimated five million adults (NINDS, 2009). Although a deficit in episodic memory is the most familiar symptom, language disturbance is also a core marker for AD (McKhann et al., 1984; Weiner et al., 2008). Typically, AD patients experience increasing word-finding and language comprehension difficulties as the disease progresses. The toll of these deficits has recently spurred advances in treating associated language impairment (Bayles & Kim, 2003; Gonzalez Rothi et al., 2009). Yet, much remains unclear about cognitive-linguistic functioning in AD.

Phonology in Alzheimer's disease

The dominant theoretical position is that phonological processing is well preserved until late stages of AD. Empirical support for this assumption has been derived from studies showing that speech production in AD is similar to healthy control participants on tasks such as reading orthographically regular words aloud, and producing connected speech (Bayles & Tomoeda, 1983; Lambon Ralph et al., 1995).

A number of researchers have, however, questioned the assumption of intact phonology in AD. Studies of spoken-word recognition have demonstrated lexical discrimination difficulties with frequent phonological confusions (e.g., *doll* for *dog*) that worsen during the course of the disease and become especially evident for words that have many similar-sounding neighbors (Eustache et al., 1995; Sommers, 1998). AD patients also poorly accommodate acoustic variability in their speech perception across speakers. The ability to effectively compensate for these variations, known as *talker normalization*, allows normal listeners to flexibly apply their knowledge of invariant acoustic cues in order to correctly perceive *cat* whether it is spoken

by a New York cabdriver or a toddler in Georgia. The normalization deficit in AD is apparent when more advanced AD patients fail to discriminate words presented in succession produced by speakers of different ages, genders, and dialects (Sommers, 1998).

Other work has demonstrated phonological output deficits in AD that manifest as speech errors (Cuetos et al., 2003; Glosser et al., 1998; Glosser et al., 1997). In one study, AD patients repeated sentences of increasing length and syntactic complexity (Biassou, et al., 1995). Patients produced significantly more pseudoword errors (e.g., the cat *popped* the balloon → the cat *plopped* the balloon), word initial errors, and phonemic substitution errors than controls. The authors attributed this particular error pattern to a deficit in lexical-phonological retrieval.

Croot and colleagues examined repetition, naming, and connected speech in a sample of 10 AD patients selected specifically for their phonological deficits. They argued for variability in etiology, extending from phonetic encoding to degraded lexical-phonological knowledge (Croot et al., 2000). In conversational speech, phonological paraphasias composed 39.1% of all speech errors; patients also made phonemic errors in repetition and naming and in reciting overlearned material (e.g., days of the week, the alphabet). Six of the 10 patients in the Croot et al. sample had autopsy-confirmed Alzheimer's pathology with damage to perisylvian structures critical for speech production. The authors note that focal perisylvian damage is an atypical presentation for AD, and thus the extent to which these phonological errors are present in AD patients as a whole is not clear.

Semantic memory in Alzheimer's disease

Our laboratory has proposed a two-component model of semantic memory based on the dynamic interaction between knowledge and process (Koenig & Grossman, 2007). We will interpret semantic memory deficits throughout this review in terms of this model. We argue that conceptual representation depends on two overarching and at least partially neuroanatomically dissociable processes: (i) stored semantic feature knowledge, i.e., *content*; and (ii) dynamic integration of these stored features via categorization, i.e., *process* (Koenig et al., 2007).

Concrete concepts (e.g., CAT) are composed of features, and functional imaging studies suggest that semantic features are stored in or near modality-specific regions of cortex. For example, storage of visually salient semantic features such as color and form relies heavily on cortical regions proximal to the ventral temporal-occipital visual pathway (Bussey & Saksida, 2002; Humphreys & Riddoch, 2006; Martin & Chao, 2001), whereas auditory features are stored in areas of superior temporal cortex (Beauchamp, 2005; Binder et al., 1996), and manipulability/functional features are stored in inferior frontal, premotor, and parietal cortex (Grossman et al., 2008; Pulvermuller, 2001).

Semantic processing involves rapid categorization and binding of features from different sensory modalities (e.g., barking, slobbering, furry) with abstract propo-

sitional knowledge (e.g., is friendly) into a single cohesive concept (DOG). Several candidate brain regions for semantic integration include multimodal association cortex in the lateral temporal lobe (superior temporal sulcus) and posterior temporoparietal cortex (i.e., angular gyrus) (Beauchamp, 2005; Murtha et al., 1999). Other researchers have strongly argued that feature convergence occurs primarily in the temporal poles (Joubert et al., 2009; Lambon Ralph et al., 2001; Rogers, Hocking et al., 2006; Rogers et al., 2004).

Neural structures dedicated to processing, active maintenance, and inhibitory control of competing concepts include frontal lobe regions such as dorsolateral prefrontal cortex and left inferior frontal gyrus (Thompson-Schill et al., 1997; Wagner, Desmond et al., 1998). Anatomical regions critical for semantic processing are affected early during the course of AD as demonstrated through decreased resting fluorodeoxyglucose (FDG) uptake via positron emission tomography (PET) (Zahn et al., 2006). Converging evidence has been reported via voxel-based morphometry (Grossman et al., 2004; Joubert et al., 2009), perfusion imaging (Grossman, Koenig, Glosser et al., 2003), and postmortem tissue volume studies (Harasty et al., 1999). Many of the same studies have also documented damage to regions important for semantic storage, most notably the temporal neocortex, temporopolar region, posterior fusiform gyrus, and premotor cortex. Thus, one biologically plausible hypothesis based on the frontal-temporal distribution of cortical damage in AD is that semantic memory deficits reflect damage to *both* process and content in semantic memory. This process–content hypothesis remains controversial as some researchers have argued for the differential weighting of either process or content (Aronoff et al., 2006; Rogers & Friedman, 2008), whereas others have argued exclusively for process-based impairment that affects semantic access (Bayles et al., 1991; Ober & Shenaut, 1999). Yet others have argued for specific degradation of semantic content (Hornberger et al., 2009).

Substantive evidence for degraded semantic memory in AD has been derived from word association and naming tasks in which patients show disproportionate impairment in semantic category fluency (e.g., the number of animals listed in 60 seconds) relative to letter-naming fluency (e.g., the number of words beginning with the letter “F” listed in 60 seconds) (Adlam et al., 2006; Salmon et al., 1999). AD patients also show reduced semantic priming effects in word-stem fragment completion (e.g., cat → d-?) (Passafiume et al., 2006) and reduced word frequency effects in free association (e.g., bride → ?) (Gollan et al., 2006). Degraded semantic knowledge is also apparent in nonverbal domains such as demonstrating appropriate functions of common objects (Chainay et al., 2006) and sorting pictures into appropriate categories such as tool–animal or domesticated–wild (Aronoff et al., 2006; Salmon et al., 1999). In summary, there is compelling evidence to support core semantic knowledge deficits in AD. However, the organization and degradation of semantic memory remains controversial. This is especially true with respect to category-specific semantic impairment that is characterized by the apparent loss of some semantic categories (e.g., animals or tools) with relative preservation of other categories.

Items within the same superordinate category (e.g., ANIMALS) tend to have greater semantic feature intercorrelation (e.g., tail, fur, etc.) than items between semantic categories (Garrard et al., 2001; Rogers et al., 2004). For example, many TOOLS have serrated edges, whereas ANIMALS have tails and legs. High feature density has the advantage of facilitating categorization but also the disadvantage of requiring finer-grained processing of distinctive features to distinguish among coordinate category members. In the face of a neurodegenerative disease such as AD, the feature knowledge contributing to a concept may be degraded due to the progressive loss of knowledge represented in sensory-motor cortices. This could include visual-perceptual knowledge, for example. From this perspective, visual-perceptual feature knowledge plays a heavily weighted role in the meaning of categories consisting of natural kinds, and progressive loss of this kind of knowledge can mimic a category-specific semantic memory impairment. Alternately, there may be preferential degradation of feature knowledge that is distinctive. Many have theorized that distinctive features are particularly vulnerable to AD (Chertkow & Bub, 1990; Duarte et al., 2009). It follows that as distinctive features are lost, patients “average” coordinate concepts into a prototype or central tendency that is representative of the category. Thus, patients may be likely to produce coordinate naming errors such as “dog” for “cat” and may also progress toward naming at a higher taxonomic level, producing “animal” for “cat.” This may lead to a category-specific semantic memory impairment because of the differential density of the concepts in these semantic fields. Both of these hierarchical error types have been reported in AD. We have argued that concepts have distributed representations within a semantic memory system that is largely undifferentiated by semantic category (Grossman et al., 2002). We return to the concept of category specificity in the section to follow.

Naming in Alzheimer’s disease

The distribution of neuropathology in AD suggests multiple potential sources of disruption along the naming pathway. One hypothesis is that perceptual deficits in AD interfere with naming at a pre-semantic stage of visual object recognition. Other possibilities include lexical retrieval difficulties and “downstream” deficits that disrupt phonological encoding. Although difficulties exist at these perceptual and lexical levels of processing in AD, careful analyses of naming error distributions reveal predominance of semantic errors relative to phonemic or visual errors. Figure 12.1 represents the distribution of errors we recently found in AD relative to the two other patient groups described later in this review, progressive non-fluent aphasia (PNFA) and semantic dementia (SD). These errors reflect ratios of specific error types elicited by naming a set of 60 black-and-white line drawings within a sample of 36 AD patients. The most frequent error in this patient sample was semantic, constituting 19% of all naming errors.

A semantic basis for anomia in AD is further supported by studies that have demonstrated strong correlations between residual conceptual knowledge and

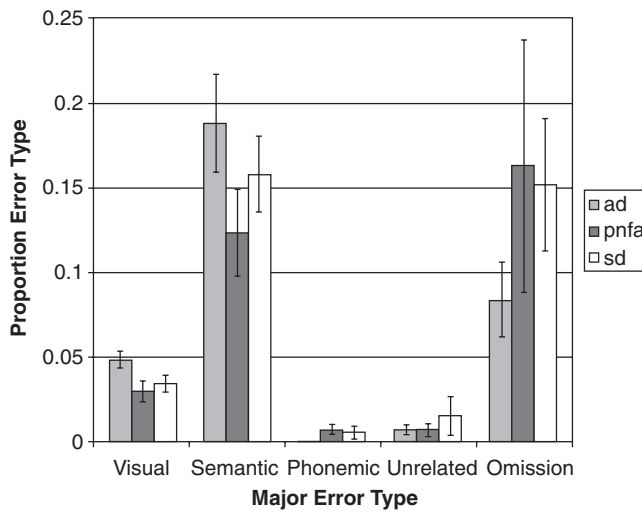


Figure 12.1 Major naming errors in SD, AD, and PNFA

naming ability. Hodges and colleagues (1996) examined the correlation between “naming and knowing” via quality of concept definitions. The majority of AD patients (76%) showed significant naming impairment relative to controls. Sixty percent of items that were correctly named were also defined in a way that the authors argued captured the core concept of the referent. In contrast, significantly fewer correct definitions were provided for items patients were unable to name (<30% correct). The correlation between naming and knowing in AD has also been demonstrated in nonverbal domains including picture sorting and semantic feature verification, thus ruling out isolated lexical impairment (Aronoff et al., 2006; Garrard Lambon Ralph et al., 2005; Salmon et al., 1999).

One of the most fiercely contested aspects of language processing is category specificity, in which items from a particular semantic category are differentially impaired. The most common category deficit in AD occurs for naming biological natural kinds such as animals and fruits relative to manufactured artifacts (Gonnerman et al., 1997; Whatmough et al., 2003). We have argued that this category effect reflects loss of distinctive feature knowledge that is necessary for distinguishing natural kinds (Grossman, Koenig et al., 2007). Support for this hypothesis is derived from double dissociations observed in naming manufactured artifacts and natural kinds in AD (Gonnerman et al., 1997).

Gonnerman and colleagues hypothesized that cortical damage in AD ultimately results in a “crossover” naming impairment, with initial deficits that present as impairment in natural kinds due to vulnerability of distinctive features, and later evolving toward deficits in artifacts due to greater resilience of shared features to brain damage. This crossover from natural kinds to artifacts awaits definitive support from a larger sample of patients. In one larger study ($n = 72$), however,

Whatmough and colleagues found that anomia for natural kinds was worse across all levels of AD severity (Whatmough et al., 2003). The authors argued in accord with *sensory-functional theory* that, rather than a specific segregation of natural kinds and artifacts, these category effects reflect disproportionate impairment to temporal lobe structures that support sensory information (e.g., color, form) relative to a frontoparietal distribution of brain structures that supports knowledge of object function and manipulability.

Grammatical processing in Alzheimer's disease

AD patients have sentence comprehension difficulties. A persistent challenge involves disentangling syntactic processing deficits from other co-morbid difficulties that affect sentence comprehension. Some researchers have argued that genuine syntactic deficits are apparent in AD (Grober & Bang, 1995). Others have hypothesized that many apparent syntactic deficits reflect methodological artifact. For example, the integrity of grammar is often probed by asking patients to make acceptability judgments of sentence structures with some syntactic violation (e.g., John go store). Such "offline" measures require a patient to hold a sentence in working memory until they can make a metalinguistic judgment of its acceptability. This process relies on a notoriously fragile memory system in AD. Thus, one strong position is that "post-interpretive" working memory deficits underlie difficulties with offline measures of grammatical ability in AD (Waters & Caplan, 1997).

Kempler and colleagues compared performance of AD patients via both offline and online measures of grammatical ability (Kempler et al., 1998). Their offline measure was a sentence–picture pointing varied by sentence type. Sentences differed in grammatical complexity from canonical (simple structures) to non-canonical (complex) structures. Sentences were either (i) active voice (e.g., The boy kicked the girl . . . Who kicked?); (ii) active voice with conjoined noun phrases (e.g., The boy kicked the girl and the dog); (iii) passive voice (e.g., The boy was kicked by the girl.); or (iv) active voice with a relative clause (e.g., The boy kicks the girl that chases the dog). AD patients performed worse than controls across all conditions; however, their performance with passive and conjoined sentences (conditions i and ii) was similar. Patients with classic agrammatism show deficits in comprehension of passive sentences. In contrast, patients with AD were not significantly more impaired on passives than with the simpler active conjoined sentences. The authors argued accordingly for a working memory locus over a specific syntactic impairment in AD. Further evidence for an underlying working memory impairment was presented by Kempler et al.'s online task, crossmodal naming. The dependent measure was reaction time for naming a target word in the presence of a syntactic violation (e.g., John go store). Healthy adults are slower to name *store*, for example, in a syntactically anomalous sentence environment. AD patients also showed reaction time differences, suggesting continued sensitivity to grammatical structure.

Another line of research has investigated the role of degraded verb knowledge in sentence processing. Verbs act as the director of a sentence, dictating argument structure and thematic relations between other elements. For this reason, verb deficits can grossly impair sentence processing. Studies have demonstrated a small but consistent disadvantage for comprehension and naming of verbs relative to nouns in AD (Cappa et al., 1998; Grossman, Koenig, DeVita et al., 2003; Grossman & White-Devine, 1998). One methodological difficulty, however, is that verbs and nouns generally differ semantically and grammatically. Naming is an insufficient index for discriminating the locus of verb impairment. We attempted to tease apart semantic from grammatical factors underlying verb deficits in AD via an online word-monitoring task in which patients responded as quickly as possible when they heard a specific word (Price & Grossman, 2005). Unbeknownst to the patient, the target word (represented in capital letters in these examples) appeared in either (i) a grammatically anomalous context in which verb transitivity was violated (e.g., The boy sleeps the CAT); (ii) a semantically anomalous context in which thematic roles were violated (e.g., The milk drinks the CAT.); or (iii) a grammatically and semantically acceptable sentence (e.g., The boy kicks the CAT). Normal adults are slower to respond when a target word appears in the presence of a semantic or grammatical violation (Marslen-Wilson & Tyler, 1980). AD patients showed similar sensitivity via reaction time differences to the transitivity violation, thus demonstrating sensitivity to grammatical properties of verbs. However, patients failed to show the same reaction time discrepancies for thematic role violations, suggesting impairment at the level of verb semantics.

We were able to validate these findings in a lexical acquisition experiment where we explicitly taught patients the novel verb, *lour*, in a naturalistic manner (Grossman, Murray et al., 2007). *Lour* is an archaic but nonetheless real English verb that denotes a frowning expression with clear disapproval. Patients were exposed to the meaning and grammatical properties of *lour* via a narrated picture story involving a badly behaved little girl. The final scene of the story linked the word with the image of an angry father, "Louise sees her father lour at her." AD patients showed significant impairment learning the semantic properties of the verb as illustrated by poor performance on word–picture matching. They were, however, not impaired in acquisition and retention of the grammatical subcategory suggesting impairment with semantics and not grammar.

Discourse Processing in Alzheimer's Disease

The most striking examples of narrative dissolution come from public figures diagnosed with AD. Perhaps the most famous study of AD narrative was reported by Gottschalk et al. (1988), who examined thematic, grammatical, and pragmatic content of Ronald Reagan's presidential debates in 1980 and 1984 via a standardized neuropsychological measure known as the *Gottschalk–Gleser Cognitive Impairment Scale* (Gottschalk et al., 1988). The authors identified cognitive impairment that

worsened in the interval between Reagan's first and second terms (1980–1984), leading ultimately to the controversial claim that Reagan experienced active symptoms of AD throughout his presidency.

A more systematic opportunity to examine narrative discourse is afforded by British author, Iris Murdoch (1919–1999), who produced her final novel, *Jackson's Dilemma*, during the early stages of AD. *Jackson's Dilemma* diverged from the quality of Murdoch's previous novels and was panned by literary critics at the time of its publication in 1995. Peter Garrard and colleagues analyzed form and content of *Jackson's Dilemma* using two of Murdoch's previous novels as baselines (Garrard, Maloney et al., 2005). Interestingly, syntactic structure was similar across all three novels. However, large differences emerged in an index of lexical diversity known as type–token–ratio (TTR), a figure that reflects the number of distinct words divided by the total number of words in a given sample. TTR was significantly reduced in *Jackson's Dilemma* relative to Murdoch's previous novels, indicating repetitive use of a smaller set of words. Garrard et al. argued that this discourse pattern reflected lexical impoverishment in the context of generally preserved syntax.

Controlled analyses of AD discourse have demonstrated impairment across a number of domains. Some studies have demonstrated difficulties in maintaining global connectedness necessary for a cohesive storyline, whereas others demonstrate impairment at the level of semantic propositional knowledge (Ehrlich et al., 1997). Common themes throughout AD discourse are excessive repetition of content, poor organization and circumlocutions (i.e., describing things instead of naming them). These deficits culminate in discourse that is most often described as fluent but empty (Tomoeda & Bayles, 1993; Tomoeda et al., 1996).

Semantic Dementia

SD is a variant of FTD linked to a specific distribution of cortical atrophy that affects anterolateral and ventral temporal cortex in the left hemisphere greater than right, later spreading to posterior and lateral temporal lobe structures bilaterally (Galton et al., 2001; Mummery et al., 2000; Snowden et al., 1989). Insidious language impairment (i.e., anomia) in the absence of a focal neurological insult is one of the earliest diagnostic features of SD (Neary et al., 1998). In the early stages of SD, patients may show worse impairment for words relative to pictures. This impairment later evolves into an apparent amodal conceptual disorder that persists regardless of representational format (e.g., pictures, words, sounds, odors, etc.) (Lambon Ralph et al., 2001).

SD patients show striking conceptual loss in the context of preserved functioning in domains such as phonology, syntax, and visual-spatial perception. Our laboratory has proposed a cognitive-linguistic model of SD, hypothesizing that support for language in this population degrades in a top-down manner, beginning with semantic, extending through lexical, and ultimately impacting phonological representations (Reilly Cross et al., 2007; Reilly et al., 2005). Figure 12.2 (plate section)

represents this cognitive model. Circumscribed brain damage isolated to ventral and inferolateral temporal cortex early in SD affects semantic knowledge. As atrophy compromises lateral temporal cortex and spreads posteriorly, patients experience lexical degradation. Finally, in the latest stages of SD, auditory perception and phonological storage are compromised. We reference this model in the review of SD to follow.

Phonology in semantic dementia

Patients with SD typically produce fluent, well-formed speech, as noted in many case studies (Hodges et al., 1995; Hodges et al., 1992; Neary et al., 1998; Snowden et al., 1989). Although SD patients do produce generally fluent speech, there has been little direct empirical support for preserved phonology. One line of research has inferred preserved phonology from repetition ability. That is, SD patients repeat single words with high accuracy (Knott et al., 1997). Yet, as the length of word lists increases, SD patients have been observed to make phoneme migration errors (e.g., dog, wheel, ship → dog, eel, whip), Patterson and colleagues have proposed the *lexical-semantic binding hypothesis* to account for this effect, arguing that word meaning acts as a glue that binds the constituent phonemes of words together (Knott et al., 1997). By this binding account, as conceptual support for language degrades, patients are more likely to make phoneme transposition errors. Although this phoneme migration effect has been reported in word-list recall, it is not always apparent and does not occur in spontaneous speech in SD (Reilly et al., 2005).

Another inference for preserved phonology in SD is found in patterns of reading aloud. SD patients show a consistent pattern of surface dyslexia, in which they can successfully read orthographically regular words (e.g., cat), but show marked impairment for irregular words (i.e., words with imperfect letter-sound correspondence such as yacht) (Cipolotti & Warrington, 1995; Patterson & Behrmann, 1997; Patterson & Lambon Ralph, 1999). Models of reading account for surface dyslexia in different ways. One common thread is that surface dyslexia reflects a reduced contribution of word meaning and over-reliance upon direct grapheme-to-phoneme conversion (i.e., converting letters directly to sounds). Thus, surface dyslexia has been described as “reading without semantics” (Shallice et al., 1983; Woollams et al., 2007).

Focusing on the anatomical distribution of the disease may also improve understanding of the cause of surface dyslexia in SD. One recent study measured the activation in the brains of SD patients using functional magnetic resonance imaging (fMRI) relative to controls while reading words with low-frequency atypical letter-sound correspondence (e.g., chassis) and pseudowords (e.g., doost, bonverse) (Wilson et al., 2009). During the reading of pseudowords, the left intraparietal sulcus was equally activated in both controls and SD patients. During reading of the low-frequency atypical words the same left intraparietal sulcus was activated in SD patients as with pseudowords, whereas the controls showed no significant fMRI

activation in this area. This finding led the researchers to hypothesize that at a neural level SD patients were treating low-frequency atypical words as pseudowords, which indicated they were not able to access the semantics of the word. It should be noted, however, that other researchers have focused on the anatomical distribution of disease, hypothesizing that surface dyslexic errors emerge as cortical atrophy spreads posteriorly in ventral temporal cortex resulting in the compromise of high-level visual perception (Glosser et al., 2002).

Beyond repetition and surface dyslexia, there have been few systematic investigations of phonology in SD. Kwok and colleagues (2006) examined phonemic perception in SD and found that patients categorically perceive the acoustic shift in voicing that marks specific consonant boundaries (e.g., “pa” vs. “ba”) similar to healthy adults (Kwok et al., 2006). Reilly et al. (2007) extended this work and examined auditory discrimination via same–different judgments for pairs of pure tones varied by frequency (1000 Hz vs. 900 Hz) and discrimination of consonant–vowel bigrams (“ba” versus “ga”). SD patients showed subtle difficulties in detecting frequency differences in pairs of pure tones. Furthermore, patients with advanced SD paradoxically performed better than milder patients in bigram discrimination, a trend the authors attributed to reduced lexical interference as the disease progresses (Reilly, Cross, et al., 2007).

Semantic memory in semantic dementia

SD presents with perhaps the strongest *in vivo* model for examining degraded object knowledge in the context of preserved functioning in other linguistic domains. We review several positions and ultimately interpret this impairment via our two-component model of semantic memory described earlier in this review.

SD patients show similar performance on word-versus-picture tasks and in making object decisions when features are presented in an auditory-versus-visual format (e.g., telephone ringing vs. picture of telephone) (Garrard & Carroll, 2006). Such item consistency distinguishes SD from other forms of aphasia, wherein patients show clear deficits for words over pictures, and also from visual agnosia, where patients show the opposite trend. This agnosia–aphasia double dissociation is critical, as one theoretical position holds that semantic deficits in SD mask a combination of aphasia and visual agnosia due to the dual compromise of left hemisphere language areas and ventral temporal-occipital structures that comprise the putative “what” pathway of visual object recognition (Mesulam, 2001, 2003).

Other researchers have argued that rather than a combination of agnosia and aphasia, SD presents with a modality-neutral deficit that results in the progressive degradation of amodal knowledge (Bozeat et al., 2000; Coccia et al., 2004; Patterson, Nestor et al., 2007; Rogers, Hocking, et al., 2006). One view of semantic degradation in SD is that anterior inferolateral temporal cortex acts as a binding site or convergence zone for disparate semantic features stored in modality-specific regions of cortex (Damasio et al., 1996; Jefferies & Lambon Ralph, 2006; Lambon Ralph &

Patterson, 2008). According to this view, damage to temporal cortex causes “binding” deficits that result in a progressive loss of knowledge, beginning with specific exemplars (e.g., dog) and later extending to entire superordinate categories (e.g., *animal*).

We argue that semantic deficits in SD begin with damage to visual association cortices degrading knowledge of visual features. Indeed, since visual feature knowledge plays a critical role in the representation of concepts, this may give the appearance initially of an amodal deficit or in fact may compromise semantic memory in a modality-neutral manner. This is due to the fact that conceptual meaning is heavily grounded in visual feature knowledge. We hypothesize that as the disease spreads to the homologous regions of the right hemisphere and dorsally to auditory association cortex and the superior temporal sulcus where auditory features of concepts may be represented, the semantic memory impairment in SD progresses and eventually may become amodal.

Tyler and colleagues (2004) have demonstrated that ventromedial anterior portions of the temporal lobe (i.e., perirhinal cortex) are recruited when fine-grained semantic discrimination is necessary between items, whereas only caudal structures are necessary for making superordinate distinctions between the same items (“Is this an animal or tool?”). This perspective on semantic specificity appears to fit well with both the distribution of cortical damage in SD and the hierarchical organization of semantic memory in normal adults. SD patients typically show impairment for distinguishing between basic-level concepts, tending to make coordinate and superordinate semantic naming errors (e.g., CAT → DOG or CAT → ANIMAL) (Grossman et al., 2004; Hodges et al., 1995). The same hierarchical taxonomic loss is evident in concept definitions and in delayed picture drawing, where SD patients have been observed to assign prototypical features to a particular exemplar (e.g., adding four legs to a duck because most category members of ANIMAL share this feature) (Bozeat et al., 2003).

Further evidence for a differential weighting of visual feature knowledge comes from performance on concrete versus abstract words in SD. Among normal adults, concrete words (e.g., dog) are earlier learned, better recalled, and more rapidly identified than abstract words (e.g., love) (Kroll & Merves, 1986). Many psycholinguists have argued that this *word concreteness effect* results from the additional visual perceptual salience associated with concrete words. SD patients show an atypical pattern known as *reversal of the concreteness effect* characterized by a selective impairment for concrete words with relative preservation of abstract words. This effect has been reported in naming (Breedin et al., 1994; Warrington, 1975), word-to-definition matching (Yi et al., 2007), narrative performance (Bird et al., 2000), lexical decision latency (Reilly et al., 2006; Reilly, Peelle et al., 2007), and single-word semantic judgments of concreteness (Reilly, Cross, et al., 2007). We and other researchers (Macoir, 2009; Vesely et al., 2007) attribute reversal of the concreteness effect in SD to the degradation of visual-perceptual feature knowledge associated with disease in visual association cortex. Difficulty with concrete relative-to-abstract concepts on a two-alternative forced-choice word associativity task correlated with right anterior temporal atrophy (Bonner et al., 2009). This is consistent

with our view of the heavy weighting of visual feature knowledge in human semantic memory.

Naming in semantic dementia

It is widely acknowledged that anomia emerges early during the course of SD (Hodges et al., 1992). Yet, the nature and etiology of this naming deficit remains quite controversial. One argument holds that naming deficits in SD reflect impaired lexical retrieval from a relatively intact semantic system (Mesulam, 2003). Evidence for this hypothesis is derived from patients with early SD who demonstrate appropriate use of objects they cannot name and show discrepant performance on picture versus word versions of semantic batteries. Differential verbal versus visual performance in early SD has also been used to advance “multiple semantics” theories that assume the existence of separate verbal and visual semantic systems subject to dissociable decline in SD.

At the heart of this debate is the issue of whether naming deficits in SD are underpinned by a central semantic loss. Patterson and colleagues have advanced the theory that semantic anomia does indeed reflect degraded knowledge by demonstrating that patients produce richer concept definitions for successfully named objects over empty descriptions of objects for which they are anomic (Lambon Ralph et al., 1999). In line with this theory, a second hypothesis is that SD patients show a strong frequency-by-typicality interaction in their naming ability. That is, highly frequent words that are prototypical examples of their respective semantic categories are better named (Patterson, 2007). For example, SD patients may be more likely to correctly assign the name DOG to a Labrador Retriever, whereas they err with infrequent and atypical category exemplars, calling a Chihuahua a CAT.

By default, healthy adults name objects at a basic level of specificity (e.g., DOG), as opposed to a subordinate (e.g., LABRADOR), superordinate (e.g., ANIMAL), or a specific exemplar (e.g., FIDO). Some theorists have argued that semantic naming errors in SD demonstrate the progressive “bottom-up” loss of a hierarchically organized semantic system. Error analyses, for example, have shown a preponderance of superordinate and coordinate errors, suggesting increased reliance on residual superordinate knowledge with loss of fine-grained specificity within categories (Lambon Ralph et al., 2001). Although this hypothesis is intuitively appealing, we recently conducted a naming error analysis and found that SD patients made few superordinate semantic errors (Reilly et al., in press). Patients in our study named 60 black-and-white line drawings from the Snodgrass and Vanderwart picture series (Snodgrass & Vanderwart, 1980), and by far the most common error SD patients produced was functional associative (e.g., hammer → “I know that thing . . . you hit with it”). We hypothesize that the prevalence of this naming error reflects a reliance on residual contextual and functional knowledge, which may be represented in frontal and parietal cortices that are relatively spared during the early stages of SD (Snowden & Neary, 2002). Further evidence for contributions of preserved fron-

toparietal structure to naming in SD comes from a study where we correlated naming performance with regional gray matter atrophy in SD via voxel-based morphometry (Grossman et al., 2004). SD naming deficits correlated strongly with atrophy in inferior and middle temporal gyri situated posterior to the temporal pole.

Grammatical processing in semantic dementia

SD patients produce empty but nonetheless syntactically well-formed utterances, leading to the assumption that grammatical aspects of language remain intact until late stages of the disease (Snowden & Neary, 2002). Although SD patients show clear deficits in sentence comprehension, the theoretical consensus is that this impairment stems from lexical-semantic impairment. That is, if one fails to comprehend the meaning of individual words within a sentence, that person will also fail to comprehend the sentence. Further evidence for preserved syntactic knowledge is evident by the frequent use of function words (e.g., the) and high-frequency verbs (e.g., go) in spontaneous speech (Bird et al., 2000).

Empirical evidence for preserved grammatical knowledge in SD is derived from two studies conducted by our laboratory. In one of these studies, we employed an auditory word-monitoring paradigm in the context of a syntactic anomaly. Normal listeners are slower to identify a target word (e.g., ball) when it occurs in the presence of a grammatical violation (e.g., John foots the ball) (Marslen-Wilson & Tyler, 1980). SD produced the same effect, showing lengthier reaction times to recognize words in the presence of a grammatical violation, suggesting continued sensitivity to this property.

SD patients also showed evidence for grammatical preservation in a recent lexical acquisition experiment where we explicitly taught patients the novel verb, *lour*, in a naturalistic manner (Murray et al., 2007). For more detail on this experiment, we refer the reader to our earlier discussion of grammatical processing in AD. SD patients showed significant impairment learning the semantic properties of the verb as illustrated by poor performance on word–picture matching. We also probed grammatical knowledge of *lour* and found that SD patients were impaired at distinguishing between the use of *lour* as a verb or a noun, although they were somewhat better at detecting violations of thematic matrix. Patients also correctly rejected *lour* when it was presented as a closed-class word such as a preposition (e.g., He ran *lour* the hall). These results suggest difficulty with lexical-semantic processing in the context of sensitivity to the major grammatical distinction between closed- and open-class words.

Discourse processing in semantic dementia

SD patients experience semantic impairment that manifests as severe anomia at the single-word level. Perhaps, for this reason, studies of SD discourse are exceedingly

rare. In one study, Bird and colleagues (Bird et al., 2000) examined dissolution of narrative discourse in SD via descriptions of the *Cookie Theft Picture*, a complex scene depicting a kitchen in disarray (Goodglass & Kaplan, 1983). The authors assessed performance of three SD patients at three different times during their decline. Speech rate among patients was comparable to age-matched controls. However, patients showed marked differences in the content of their production, tending to progressively lose low-frequency, high-imageability words (e.g., spatula), while retaining highly frequent closed-class words (e.g., the) and verbs (e.g., go). Thus, patients tended to produce increasingly empty and abstract narratives as SD worsened.

Sharon Ash and colleagues (2006) conducted one of the most detailed study of SD discourse published to date, asking patients ($n = 13$) to narrate the wordless children's picture book, *Frog, Where Are You?* (Mayer, 1969). Each page in this text depicts a plot twist in the adventure of a boy in search of his pet frog. This method of eliciting a narrative has many advantages over a description of a single static picture, including the ability to examine cohesion, global connectedness, and the gist of the story, referencing of temporally remote events, and conveying specific semantic content within different scenes. SD patients had difficulties narrating the story. Their verbal fluency was reduced relative to controls (SD = 81 words per minute (wpm); controls = 142 wpm), and patients often omitted or gave nonspecific references to items they could not name (e.g., "that thing"), a trend that reduced the specificity of content throughout the story. Additional naming errors were found, including the production of nonspecific pronominal references (e.g., "he" for the boy, dog, and frog) and general superordinate terms (e.g., "animal" or "critter" for "dog" or "frog"). Despite difficulties in lexical retrieval, patients were able to demonstrate reasonable global connectivity across the episodes of the story, suggesting preserved gist knowledge. In a companion study, Ash and her co-workers (2009) associated reduced fluency during narrative performance to a semantic deficit.

Meteyard and Patterson (2009) conducted a study in which they analyzed the naturally occurring speech of SD patients during interviews of autobiographical memory. They found that SD patients were more likely to make open-class word (e.g., nouns, verbs) substitution and omissions and closed-class word (e.g. the, it, is) substitutions as compared to controls. These findings led the researchers to hypothesize that a minor syntactic deficit was present. It should be noted, however, that the researchers still point to semantic degradation as the largest contributing factor to deficits in discourse.

Progressive Non-Fluent Aphasia

Arnold Pick (1892) described a patient with progressive deterioration in personality and social comportment who subsequently developed a reduction in speech fluency that eventually led to complete mutism. The next year, Serieux (1893) likely described

the earliest case study of a syndrome today known as progressive non-fluent aphasia (PNFA). PNFA is currently recognized as a variant of FTD characterized by cortical atrophy that affects inferior frontal and anterior perisylvian regions critical for speech production (Nestor et al., 2003). PNFA is so named because of its phenotype, describing a progressive decline in speech fluency; however, these patients do show deficits in other aspects of language, including phonemic and grammatical processing.

Phonology in progressive non-fluent aphasia

One of the most striking behavioral features of PNFA is the presence of halting and effortful speech. PNFA patients often experience co-morbid apraxia of speech (AOS) and dysarthria, and their speech is slow, hypophonic, and dysprosodic (Brambati et al., 2009; Kertesz et al., 1994; Ogar et al., 2007; Thompson et al., 1997). As noted earlier, the progressive decline of speech in PNFA often leads to mutism. Gorno-Tempini and colleagues (2006) investigated the neural basis for early mutism in PNFA, contrasting gray matter atrophy of mute with non-mute PNFA patients via voxel-based morphometry (VBM). In this structural anatomical study, both PNFA groups showed atrophy in the left inferior frontal gyrus pars opercularis (posterior Broca's area), superior temporal gyrus, insula, and precentral gyrus. Additionally, mute PNFA patients had atrophy that extended subcortically to the basal ganglia, an area critical for timing and execution of speech (Gorno-Tempini, et al., 2006). Corroborating evidence for the disease locus of PNFA was reported by Nestor and colleagues (2003), who found FDG-PET hypometabolism (reduced metabolic activity) in left anterior insula and frontal operculum regions of a sample of non-mute PNFA patients without dementia ($n = 10$). Ogar and colleagues using VBM compared gray matter volume of PNFA patients with AOS and dysarthria to that of age-matched controls. Relative to healthy controls, there was a correlation in the PNFA patients between AOS, dysarthria, and volumetric loss in the left posterior frontal cortex and basal ganglia (Ogar et al., 2007).

A number of studies have analyzed speech production in PNFA. Croot and colleagues (1998) examined production for nouns varied by word length in two PNFA patients and found rates of phonological paraphasias (e.g., skunk → skump) in up to 46.9% of all utterances. Patients in the Croot et al. study showed benefit from phonological structure, displaying a task-by-accuracy interaction. Production was best for reading aloud (38.5% mean accuracy), followed by single-word repetition (28.75% mean accuracy), and then naming (21.55% mean accuracy). There was also a strong negative linear correlation between accuracy and word length. That is, word length negatively impacted production in these patients. In a larger and more heterogeneous patient sample, investigators reported that almost half of the utterances of these patients were distorted and/or contained paraphasic errors in a semi-structured speech sample (Ash et al., 2004). This was a significantly higher rate of

phonemic paraphasic errors than was produced by either AD or SD patients on the same task.

The studies described above involved informal characterizations of speech, without providing strict criteria for categorizing the nature of the speech errors in PNFA. Ash et al. (2010) studied digitized speech in a large series of PNFA patients. She used strict criteria to distinguish between a speech-sound error that might be related to a disorder of motor planning seen in AOS, on the one hand, and a speech-sound error related to a disorder of the phonological system. These investigators found that over 80% of the speech-sound errors produced by PNFA patients are phonemic in nature, derived from a disorder of the speech-sound system of language, although about 20% of errors were distortions of speech sounds that are not part of the English speech-sound system. One patient in the Ash series had AOS, while the remaining 16 patients did not.

The nature of PNFA phonemic deficits remains controversial. Nestor and colleagues (2003) have argued that decreased speech dysfluency in PNFA reflects a combination of agrammatism and AOS (Nestor et al., 2003), whereas others have argued that PNFA patients experience degraded phonological representations that affect encoding processes earlier in the chain of motor speech programming (Croot et al., 1998). Corroborating evidence for phonological and higher level cognitive-linguistic involvement is derived from the fact that PNFA patients show agrammatism and sentence-processing deficits not typically evident in patients with an isolated apraxia of speech but is strikingly apparent in stroke aphasia. This direct comparison to stroke aphasia was recently conducted by Patterson and colleagues (2006), who contrasted PNFA with Broca's aphasia, revealing several group differences (Patterson et al., 2006). For one, PNFA patients failed to show evidence of substantial phonological/deep dyslexia, a condition wherein reading proceeds via a semantic route, resulting in severe impairment for reading pseudowords and function words aloud (Jefferies et al., 2007; Patterson et al., 2006). In contrast, Broca's aphasics showed varying levels of phonological dyslexia. In addition, PNFA patients nearly doubled their speech rate for oral reading over connected speech, whereas stroke aphasics showed relative consistency across tasks. This pattern demonstrated phonological scaffolding in PNFA that was not apparent in Broca's aphasia. The authors concluded that PNFA deficits reflect the selective compromise of self-generated speech (Patterson et al., 2006). Although there is no definitive answer, we have argued for degradation of lexical-phonological knowledge in PNFA, consistent with damage to perisylvian regions critical for phonological encoding (Grossman & Ash, 2004).

Semantic memory in progressive non-fluent aphasia

The study of semantic memory in PNFA presents unique challenges because traditional measures of semantic ability are often confounded with impairment in other cognitive-linguistic domains. The distribution of cortical damage in PNFA affects

frontal and perisylvian structures critical for phonological working memory (Smith & Jonides, 1999), phonological output production (Poldrack et al., 1999), and grammatical processing (Friederici, 2001). Contributory deficits in each of these domains can potentially exaggerate the severity of semantic impairment. For example, PNFA patients have demonstrated gross impairment on semantic category fluency naming relative to healthy controls. Yet, these patients show comparable impairment on letter fluency tasks, suggesting a shared deficit in phonological production that impacts both tasks (Rogers, Ivanoiu et al., 2006). Based on mildly impaired performance relative to controls on receptive language tasks such as word-to-picture matching (Grossman et al., 1996) and semantic categorization of pictures and words (Rogers, Ivanoiu, et al., 2006), the theoretical consensus is that semantic memory is generally preserved in PNFA relative to either SD and AD.

The assumption of preserved semantic memory is tempered by poor performance of PNFA patients on learning paradigms recently employed in our laboratory. In these studies, AD, SD, and PNFA patients attempted to learn a novel category of fictional animals we refer to as *Crutters* (Koenig et al., 2007). Patients attempted to learn the category, CRUTTER, either through explicit rule-based instruction on semantic features (e.g., a CRUTTER has a short tail, tusks, and a spotted leg . . . Is this a CRUTTER?) or via similarity-based training relative to a prototype. Rule-based processing depends on executive resources necessary for attending to specific features and making comparisons to other exemplars via working memory. In addition, a critical aspect of rule-based processing is the ability to inhibit or suppress features that may be salient but do not discriminate between category members (e.g., Chihuahuas are small, but they are not cats). Alex Martin and others have argued that these components constitute a semantic working memory system that is localized in left inferior frontal cortex (Martin & Chao, 2001; Thompson-Schill, et al., 1997; Wagner, Poldrack et al., 1998), a region prominently affected in PNFA. In the rule-based condition of our *Crutter* experiment, PNFA patients attended to salient but incorrect semantic features such as size and color and were, thus, significantly impaired relative to controls (Koenig et al., 2006). This sharply contrasts with their remarkably accurate performance on similarity-based training, a condition with reduced executive resource demands.

Naming in progressive non-fluent aphasia

PNFA patients experience clear deficits in naming. In a recent study, PNFA patients ($n = 10$) showed a strong correlation between disease severity and anomia, correctly naming an average of 48.1 of 64 line drawings, whereas controls were at ceiling on the same stimuli (Patterson et al., 2006). If it is true that PNFA is associated with primary deficits in lexical-phonological processing and motor speech programming, one might expect their naming to be littered with phonemic paraphasias and articulatory distortions. A number of case studies have indeed reported this pattern, showing phonemic error rates up to 47% in single-word naming (Croot et al., 1998).

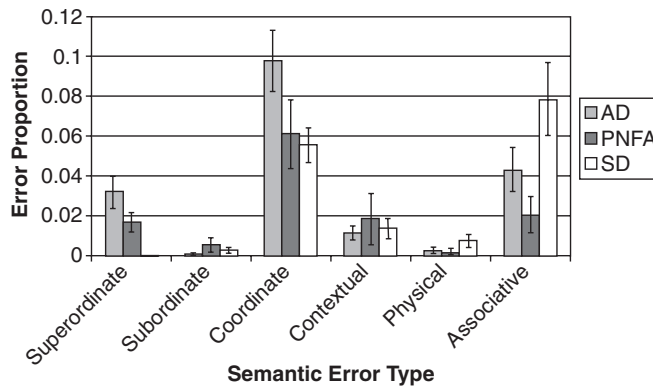


Figure 12.3 Semantic naming errors in SD, AD, and PNFA

An additional prediction is that semantic errors are unexpected in the context of grossly preserved semantic memory. This error pattern, however, was not what we found in a recent analysis of naming in PNFA (Peelle, Reilly et al., 2007). Figure 12.3 illustrates the distribution of semantic errors incurred in PNFA relative to AD and SD. Of note, PNFA patients produced similar rates of semantic error as SD patients. However, error distributions revealed a quite different pattern in PNFA compared to SD. PNFA patients showed significantly higher rates of superordinate hierarchical errors than SD patients. In contrast, SD patients produced more associative errors (e.g., hammer → “you hit with it”).

Further evidence for a language-based anomia in PNFA is derived from effects of word class. Based on the frontal distribution of cortical atrophy in PNFA, one might predict naming deficits for verbs relative to nouns. Several studies have indeed reported this naming dissociation in PNFA. Hillis and colleagues demonstrated disproportionate impairment for naming verbs (54.5% accuracy) relative to nouns (81.9%) in a sample of 15 PNFA patients (Hillis et al., 2004). An additional longitudinal PNFA case study (patient M.M.L.) demonstrated a similar graded impairment of verbs relative to nouns. However, patient M.M.L. additionally showed a modality advantage with better written than oral verb naming (Hillis et al., 2002). The authors concluded that modality effects (writing better than speaking) support a grammatical component that affects verb production in PNFA.

Grammatical processing in progressive non-fluent aphasia

Much research in aphasiology has implicated areas of inferior frontal cortex (IFC) in syntactic processing. Regions of IFC are particularly vulnerable to the distribution of PNFA, suggesting a neuroanatomical basis for agrammatism in this population. As mentioned previously, a major challenge involves dissociating grammatical from executive resource and working memory deficits. To accomplish this, we have

employed a variety of online and offline measures that probe grammatical processing in PNFA. In one study we examined grammatical processing via an online word-monitoring paradigm (Peelle, Reilly et al., 2007). That is, PNFA patients were instructed to press a key as quickly as possible when they heard a particular cue word. The target word was embedded in sentences that were either correct or had a grammatical or thematic violation. Healthy adults showed longer latencies to identify words that appear in anomalous or illegal syntactic environments. Reaction times elicited from PNFA patients, however, demonstrated insensitivity to grammatical violations (e.g., Yesterday he go to the store). Yet, the same patients showed reaction time disparities for thematic violations in which there was a mismatch between the agent and the action being performed (e.g., The milk drank the cat), a pattern that supports a preserved semantic contribution to sentence processing in the context of a reduced grammatical contribution.

The second source of evidence for grammatical deficits in PNFA is differential performance with respect to word class (e.g., verbs vs. nouns). Selective verb deficits have been reported in naming in PNFA (Cappa et al., 1998; Hillis et al., 2004). As discussed earlier, however, it is impossible to infer a pure grammatical deficit from naming. We circumvented this confound by probing semantic and grammatical knowledge distinctively via a lexical acquisition experiment wherein PNFA patients acquired the novel verb, *lour*, in a naturalistic manner through a picture story (Murray et al., 2007). For more detail on this experiment, we refer the reader to our earlier discussion of grammatical processing in SD. After the exposure period, PNFA patients demonstrated appropriate semantic knowledge of *lour* via accurate forced-choice responses on a picture–word matching task. However, they showed marked deficits relative to controls in identifying grammatical violations of *lour* (e.g., The *lour* saw the man glancing at him), providing further empirical evidence for PNFA syntactic impairment.

Discourse in progressive non-fluent aphasia

There have been few studies of discourse processing in PNFA, and the majority of these have focused on phonological and grammatical aspects of production. Patterson and colleagues, for example, examined PNFA verbal fluency via description of the *Cookie Theft Picture* from the Boston Diagnostic Examination of Aphasia (Goodglass & Kaplan, 1983; Patterson et al., 2006). PNFA production was about one-fifth the rate of controls, with average of 27.8 wpm (controls = 137.4 wpm).

We examined both form and content of narrative discourse by asking PNFA patients ($n = 10$) to narrate *Frog, Where Are You?* (Ash et al., 2006; Ash et al., 2009). In terms of speech fluency, PNFA patients produced 45 wpm, whereas controls produced an average of 142 wpm (approximately one-third the output). Additionally, patients produced sparse narratives with a substantially reduced mean length of utterance (MLU) relative to controls. MLU is an index derived by dividing the total number of words produced by the total number of utterances, thus, providing a

metric for comparing phrase length. MLU also strongly correlates with grammatical and morphological complexity (Brown, 1976). This reduction in phrase length we observed in PNFA narratives was associated with omission of function words, grammatical elements, and modifiers throughout the story (e.g., *The . . . d. .boy . . . found . . . um . . . muskrat*). Although PNFA narratives were comparatively sparse, patients performed similar to controls on measures of global connectedness, successfully conveying the gist of the story. These findings were validated by Knibb and colleagues as they also found slowing of speech and preserved global connectedness (Knibb et al., 2009). A regression analysis specifically related reduced wpm to grammatical simplification (Gunawardena et al., submitted). A VBM analysis of performance in this study related reduced wpm to cortical thinning in dorsolateral and inferior frontal cortex as well as anterior superior temporal cortex, and this overlapped with an area of cortical thinning in inferior frontal and anterior superior temporal cortex that was related to grammatical simplification.

Conclusion

In summary, we have argued that the cognitive-linguistic profiles of AD and FTD are in many ways distinctive. These unique patterns challenge the engrained assumption that language impairment in dementia reflects a generic decline in cognition. We conclude with a brief discussion of domains in which the study of language in dementia may potentially yield clinical benefits in the near future.

Diagnostic specificity

Differential diagnosis of FTD or AD can be difficult during the early stages of dementia when symptoms are mild or nonspecific. Histopathological confirmations of these conditions are rarely conducted *in vivo*. Therefore, a major challenge is to establish diagnostic criteria with high sensitivity and specificity for delineating these forms of dementia. Language is one variable that in conjunction with imaging, protein biomarker assays, and other neuropsychological measures significantly improves diagnostic specificity (Forman et al., 2006; Libon et al., 2007).

Clinical management

Patterns of survival and symptomatology associated with the clinical courses of FTD and AD differ. Behavioral management of dementia subtypes can potentially improve by better characterizing the expected cognitive-linguistic courses of these diseases. For example, if mutism is an expected outcome of PNFA, preemptive use of augmentative and alternative communication devices that produce text-to-

speech or picture-to-speech output may prolong communicative efficiency and functional independence in this population.

Behavioral targets for intervention

Language impairment remains one of the most debilitating aspects of dementia; yet, few options currently exist in terms of etiology-specific language therapies. Consequently, dementia remains a vastly underserved population. Improved specificity in delineating the nature of language impairment will improve outcomes by better tailoring interventions to meet the unique needs of each dementia subpopulation. This will allow us to more effectively target specific behavioral deficits underlying language difficulties. As an illustrative example, consider remediation of sentence-processing deficits in AD – if executive resource and working memory limitations underlie these sentence comprehension difficulties, it may be possible to facilitate comprehension by repeating and shortening utterances. In contrast, reducing or repeating utterances will have little effect if the impairment is genuinely grammatical. The same logic applies to retraining forgotten concepts. If loss of distinctive semantic features contributes to naming deficits, it may be possible to improve naming ability by retraining fine-grained semantic knowledge that distinguishes among category members (Kiran & Thompson, 2003). However, this approach will likely fail in the context of a more global loss of feature knowledge. At present, many of these issues remain unresolved, and the theoretical rationale for treating associated language impairment is weakened because behavioral targets remain vague. Thus, increased specificity may better inform the development and implementation of etiology-specific language treatments for dementia.

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