Linguistic Disruption in Alzheimer’s Disease and other Dementias

Amanda Garcia¹ and Jamie Reilly²,³

¹Department of Clinical and Health Psychology
University of Florida, Gainesville, Florida

²Eleanor M. Saffran Center for Cognitive Neuroscience
³Department of Communication Sciences and Disorders
Temple University, Philadelphia, Pennsylvania

Word Count = 5545

Address Correspondence to:
Jamie Reilly, Ph.D.
Department of Communication Sciences and Disorders
Temple University
110 Weiss Hall (265-62)
1701 N. 13TH Street
reillyj@temple.edu
Tel: (352) 672-4979
Chapter keywords: Alzheimer’s Disease, Frontotemporal Dementia, Primary Progressive Aphasia, Semantic Dementia, Language Disorder, Communication Disorder, Adult Neurogenic Disorders

**Linguistic Disruption in Alzheimer’s Disease and other Dementias**

Dementia is a non-specific term denoting a neurodegenerative condition that impacts memory, language, and other cognitive functions (Albert et al., 2011, Naik and Nygaard, 2008, National Institute on Neurological Disorders and Stroke, 2007). Although Alzheimer’s Disease (AD) is the most common dementia variant, AD is not synonymous with dementia. Numerous other forms of dementia exist, many with unique profiles of communicative impairment. Clinical neuroscience has made recent strides toward elucidating the molecular and genetic bases of many dementia subtypes. In turn, diagnostic specificity has also seen rapid improvement. A picture of complexity and diversity has since emerged with our improved understanding of the dementia variants.

Communicative disorders are ubiquitous and highly debilitating for numerous dementia subtypes. These communicative disorders can be classified based on expressed language impairments or based on histopathology of the brain. Here we elucidate the difference between these two classification systems, describing typical clusters of language impairment found in patients with neurodegenerative diseases (i.e. Primary Progressive Aphasia) as well as well as the impact of extralinguistic dementia symptoms on language functioning in certain dementia subpopulations (i.e. Alzheimer’s
Disease and Frontotemporal Degeneration). We conclude with a discussion of new directions for cognitive treatment in these specific dementia subtypes.

Primary Progressive Aphasia

There are numerous ways to describe, classify, and categorize the dementias. Two dominant classification schema involve either lumping by pathology (e.g., presence or absence of particular protein inclusions) or by phenotype (i.e., the outward manifestation of a pathological process). Primary Progressive Aphasia (PPA) is the best known taxonomy applied to the phenotype of a progressive language loss. Mesulam (1982, Mesulam, 2007) first described primary progressive aphasia (PPA) as a language-based dementia. The hallmark of this disorder is two years of progressive language impairment in the absence of generalized dementia. PPA is not typically caused by an acute stroke, trauma, or tumor. Rather, PPA is insidious and steadily progressive. Classifying the pathophysiology of PPA has presented a major challenge. PPA typically occurs during the early stages of an unspecified disease process (e.g., Frontotemporal Degeneration). Thus, patients with PPA do not typically come to autopsy until their language symptoms have evolved into more severe, generalized forms of dementia. The most extensive postmortem confirmation studies to date suggest that the majority of PPA cases (about 2/3) are caused by Frontotemporal Degeneration (FTD) protein pathology. Alzheimer’s Disease pathology contributes to about 30% of PPA cases, with the remainder secondary to other dementias (e.g., Vascular Dementia) (Grossman, 2010, Mesulam et al., 2008).
Three variants of Primary Progressive Aphasia have been described. As noted above, they are defined by clusters of symptoms, rather than neuropathology. Gorno-Tempini and colleagues delineated formal diagnostic criteria for three PPA variants: 1) Nonfluent/Agrammatic PPA; 2) Semantic variant PPA; and 3) Logopenic Progressive Aphasia (Gorno-Tempini et al., 2011). We will begin this discussion of language impairments in dementia by describing the subtypes of PPA. We will then comment on language impairments found in patients with histological evidence of dementia outside of these subvariants.

<table>
<thead>
<tr>
<th>Phenotype Classification</th>
<th>Pathology Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfluent Progressive Aphasia</td>
<td>Semantic Variant PPA</td>
</tr>
<tr>
<td>- Agrammatism and/or effortful speech</td>
<td>- Impaired confrontation naming and/or single word comprehension</td>
</tr>
<tr>
<td>- Impaired comprehension of complex sentences</td>
<td>- Impaired object knowledge</td>
</tr>
<tr>
<td></td>
<td>- Surface dyslexia or dysgraphia</td>
</tr>
<tr>
<td>- Spared:</td>
<td>- Spared:</td>
</tr>
<tr>
<td>- Single word comprehension</td>
<td>- Repetition</td>
</tr>
<tr>
<td>- Object knowledge</td>
<td></td>
</tr>
</tbody>
</table>

Nonfluent/Agrammatic progressive aphasia

Nonfluent/Agrammatic Progressive Aphasia (hereafter NFPA) is characterized by prominent agrammatism and effortful language production (Gorno-Tempini et al., 2011).
The core diagnostic criteria for NFPA include agrammatism and/or effortful speech. Supportive features are impaired comprehension of complex sentences, spared single word comprehension, and spared object knowledge. These cognitive deficits have been linked to cortical atrophy in the language dominant hemisphere. This atrophy encompasses both the classical Broca’s Area and a more extensive distribution of the left dorsolateral prefrontal cortex (Ash et al., 2009, Gorno-Tempini et al., 2011, Gorno-Tempini et al., 2004).

Patients with NFPA experience a mixture of linguistic input and output deficits, though impairments are especially striking in production. Agrammatism, for example, manifests in the use of syntactically sparse sentences and the omission of grammatical morphemes and function words (Gorno-Tempini et al., 2011, Grossman, 2012). Reduced grammatical complexity is also evident in conversational speech, wherein patients tend to produce an overabundance of canonical sentence structures (e.g., subject-verb-object) that are peppered with grammatical and morphological errors (Knibb et al., 2009). Non-linguistic cognitive deficits also contribute to their compromised sentence processing. NFPA patients experience impaired executive functioning, which may impact their ability to organize complex grammatical forms and process long distance dependencies (Ash et al., 2009, Libon et al., 2007).

Effortful speech is clearly the most striking deficit seen in NFPA. Output is marked by frequent pauses, increased effort in production, and overall slowed rate of production (Amici et al., 2006, Gorno-Tempini et al., 2011, Grossman et al., 2012). Some researchers suggest a contributory role of motor planning speech deficits such as Apraxia of Speech (AOS) in NFPA (Amici et al., 2006). Others argue that the fluency
problems these patients experience are rooted in a higher-level linguistic etiology, impacting phonological representations or phonetic encoding (Croot et al., 2012). The presence of agrammatism (a syntactic impairment) suggests the contribution of a linguistic component. Moreover, the claim of a supra-motor basis for language disturbance in NFPA is bolstered by recent work from our own lab demonstrating a preponderance of semantic naming errors in NFPA (Reilly et al., 2011b).

NFPA is also characterized by linguistic input deficits, specifically in the comprehension of syntactically complex sentences and in detecting syntactic anomalies (Amici et al., 2006, Gorno-Tempini et al., 2011, Grossman and Moore, 2005, Grossman et al., 2005). Impairment in these domains has also been linked to a complex interaction between grammatical and working memory resource deficits (Grossman and Moore, 2005, Grossman et al., 2005). Patients with NFPA typically show comprehension advantages for material presented at the single word level relative to material embedded within discourse.

Semantic variant primary progressive aphasia

In a classic study, Warrington (Warrington, 1975) described a series of patients who showed a selective impairment of semantic memory. This condition, later termed semantic dementia, is now designated as Semantic variant PPA (SvPPA). The core diagnostic criteria for SvPPA include: impaired confrontation naming and single-word comprehension; supportive features that are also commonly present include impaired object knowledge, surface dyslexia or dysgraphia, spared repetition, and spared speech production (Gorno-Tempini et al., 2011).
SvPPA is characterized by primary neurodegeneration of anterolateral portions of the temporal lobes. Cortical atrophy during the early stages of SvPPA is often asymmetric, impacting the left cerebral hemisphere. As the disease progresses, atrophy spreads to homologous right hemisphere structures, engulfing much of the temporal lobes (Lambon Ralph et al., 2001, Mummery et al., 2000, Mummery et al., 1999). This distribution of temporal lobe pathology is unique from that of Alzheimer's Disease in that SvPPA appears to somewhat spare the medial structures (e.g., hippocampus) that are crucial for episodic memory encoding. Figure 1 shows an MR image of a patient with SvPPA, illustrating temporal lobe degeneration. This figure shows slices of the brain in the axial view, presenting views of the structures in an inferior (i.e., bottom) to superior (i.e., top) manner. These slices demonstrate atrophy of the temporal poles, with relative sparing of more posterior cortices.

Damage to the lateral temporal lobes (i.e., neocortex) in SvPPA produces a severe and in many respects a rather selective impairment of semantic memory. As a result, patients with SvPPA tend to experience severe language impairments for most tasks that are mediated by semantic knowledge (e.g., naming, reading aloud orthographically irregular words). Moreover, the language impairment associated with SvPPA tends to be fairly homogeneous across representational modalities (Benedet et al., 2006, Bozeat et al., 2003, Bozeat et al., 2000, Coccia et al., 2004, Hodges, 2003, Lambon Ralph et
That is, patients with SvPPA tend to show comparably poor performance for words, pictures, environmental sounds, odors, etc. Such consistency strongly implicates damage to a central semantic store that subserves both verbal and nonverbal cognitive performance. SvPPA is of extraordinary interest to neuroscientists for the ways that the condition speaks to modularity among the systems that support language comprehension and expression. Patients with SvPPA tend to show focal deficits in semantic knowledge with relative preservation of many other cognitive domains (e.g., phonology, perceptual matching, visuospatial functioning) (Reilly et al., 2007, Reilly et al., 2005, Reilly and Peelle, 2008, Reilly et al., 2010).

SvPPA also is characterized by profound anomia with the presence of frequent omissions and superordinate semantic naming errors (e.g., ‘animal’ for dog). These errors tend to occur, however, in the context of speech that is phonologically, prosodically, and grammatically well formed. Language production is generally fluent, personality is grossly preserved, and many of the automatic, overlearned conversational pleasantries that punctuate casual discussion remain intact. Thus, it can often be quite difficult in casual conversation to detect that anything is ‘wrong’ with a person with SvPPA. Yet, impairments quickly become apparent in discourse when probing basic aspects of word and object knowledge. Language tends to be empty and circumlocutory. As disease severity worsens, such deficits are ever more apparent in nonverbal domains (e.g., pouring detergent into marinara sauce, feeding visitors non-edible plants).
Logopenic progressive aphasia (LPA)

The core diagnostic criteria for Logopenic Progressive Aphasia (LPA) are impaired lexical retrieval and poor repetition of sentences and phrases. The supportive criteria include: phonologic speech errors, spared object knowledge, spared motor speech, and absence of frank agrammatism (Gorno-Tempini et al., 2011). LPA is characterized by primary thinning of the left temporo-parietal junction, though different aspects of the syndrome have discrete neuroanatomical correlates. Confrontation naming deficits are most associated with atrophy of the inferior-posterior parietal lobe, while sentence repetition deficits are most associated with that of the posterior superior temporal gyrus (Leyton and Hodges, 2013, Rogalski et al., 2011a). As the disease progresses, this atrophy spreads to include the anterior temporal lobe and dorsal frontal cortex/inferior frontal gyri (Rogalski et al., 2011b).

Gorno-Tempini and colleagues have characterized many of the language comprehension difficulties in LPA as arising from impairments of phonological storage and articulatory rehearsal (Gorno-Tempini et al., 2008). In this way, the slow speech and speech errors observed in these patients can be thought of as qualitatively different than those observed in patients with NFPA. For example, while these patients had decreased speech rate compared to healthy older adults, this slowing can primarily be attributed to word finding problems, false starts, and filled pauses rather than a difficulty with syntactic processing (Amici et al., 2006, Wilson et al., 2010). Additionally, their confrontation naming errors primarily result from difficulty with lexical retrieval rather than loss of semantic knowledge, differentiating their performance from that of SvPPA patients. They may respond with aspects of the object (e.g. “It lives in the water,” “It’s
found in Egypt") or provide responses phonologically similar to the target (Leyton and Hodges, 2013, Gorno-Tempini et al., 2011). Speech errors produced during discourse also seem to stem from phonological rather than motor errors (Wilson et al., 2010).

Further evidence for a phonological loop disorder comes from differentially poor performance on tasks of sentences or phrases compared to single words. They have difficulty comprehending sentences, regardless of syntactic complexity, and have impaired performance on tasks of sequential commands (Amici et al., 2006, Gorno-Tempini et al., 2008). They additionally show difficulty repeating sentences or phrases, often substituting semantically similar responses for the target. For example, they may say “It looks like nobody is there” for “It looks as if nobody is around” (Gorno-Tempini et al., 2008). Their overall single word repetition, however, is mostly intact (Hodges et al., 2008, Amici et al., 2006, Gorno-Tempini et al., 2008). Thus, their impairment does not seem to result from impaired speech perception but rather from difficulty maintaining and integrating phonological information.

Histopathological Dementia Subtypes

We have thus far described several variants of PPA, or syndromes, delineated by a common set of core behaviors. One might also classify dementia subtypes via histopathological similarities such as the presence or absence of particular proteins in the brain. The following sections utilize a histopathological classification system to explain linguistic impairments found in dementia patients with different types of neuropathology. Of note, patients with the following types of dementia can, and often
do, exhibit a variant of PPA. We describe the impact of these pathologies on language functioning that may occur outside of a Primary Progressive Aphasia.

Frontotemporal degeneration (FTD)

FTD is a non-Alzheimer’s pathology linked to abnormal levels of several proteins, including tau, ubiquitin, and TDP-43 (Heutink, 2000, Neumann et al., 2006, Van Deerlin et al., 2007). A distinctive property of FTD is that the pathology tends to produce relatively circumscribed and asymmetric cortical atrophy during its early to middle stages, particularly impacting regions of the frontal and temporal lobes. The location and extent of the associated neurodegeneration mediates the qualitative nature of its associated cognitive impairment. Thus, when FTD impacts posterior frontal lobe structures in the language dominant hemisphere, patients most commonly show NFPA. In contrast, when FTD impacts regions of the temporal lobe, patients may experience SvPPA or LPA. FTD is commonly associated with language disturbance, with the exception of one FTD subtype known as behavioral variant FTD (bvFTD).

In bvFTD, progressive atrophy of anterior portions of the frontal lobes (e.g. orbitofrontal cortex) produces a variety of cognitive difficulties, including personality change, rigidity, apathy, and impaired impulse control. Patients with damage to these brain regions also experience changes in sexual behavior (e.g., hypersexuality) and eating (e.g., hyperorality), as well as a prominent dysexecutive disorder (Rascovsk et al., 2011). BvFTD is not associated with frank language disturbance. Patients with bvFTD do not experience the profound anomia seen in SvPPA or the speech production difficulties seen in NfPPA. Nevertheless, patients with this FTD variant do experience high-level
linguistic disruption, impacting macroscale elements of language production. Patients with BvFTD have difficulties with cohesion and organization of conversational narratives, with frequent tangents and poor topic maintenance (Ash et al., 2006). Patients with BvFTD have also been reported to show deficits in conversational turn-taking, comprehension of emotional language, and the production and comprehension of emotional prosody (Dara et al., 2012).

In general, bvFTD patients do not initially show the language deficits characteristic of other variants of FTD. Though their phonemic and action fluency is impaired, their performance on these measures may be associated with the increased executive demands of the task. They additionally show some impairment on other linguistic tasks with an increased executive load, such as certain types of sentence comprehension, and individual atrophy patterns may influence expression of other types of deficits such as emotional prosody.

Alzheimer’s disease

Alzheimer’s disease (AD) is the most common form of dementia, and it is among the leading causes of mortality in industrialized nations (Alzheimer's Association, 2012, Attems et al., 2005, Hebert et al., 2001). The onset of AD is strongly correlated with advanced aging. The most common association most people have with AD is that of a profound loss of episodic memory. Although episodic memory impairment is indeed a hallmark of AD, the diagnostic criteria for AD reflect a range of additional impairments that impact language and other cognitive processes that directly support communicative functioning. The most current clinical criteria for a diagnosis of AD include: (1) insidious
onset (2) history of cognitive decline (3) cognitive deficit in learning/recall and one other domain such as, language functioning, visuospatial functioning, or executive functioning. (McKhann et al., 2011).

Language disorders are commonplace in AD. Moreover, subtle linguistic deficits may be detectable during prodromal stages decades before the disease converts to frank dementia (Riley et al., 2005, Verma and Howard, 2012). The early course of AD is characterized by relatively preserved input processes critical for the perception of spoken words (e.g., phonological perception, lexical representation, grammar) (Taler and Phillips, 2008). These relatively preserved linguistic domains do, however, exist in the context of more pervasive deficits in working memory, attention, and visuospatial functioning. Thus, language comprehension tasks that tax additional memory and attentional resources (e.g., processing long sentences, processing speech in noise) often elicit comprehension breakdowns in AD (Rochon et al., 1994, Rochon et al., 2000, Waters et al., 1998). Such breakdowns highlight the complexity involved in disentangling language versus memory impairment in AD.

Relative to input processing, linguistic output is often profoundly impaired in AD. Patients with AD often have great difficulty naming single words, especially proper nouns and living things (Hodges and Patterson, 1995, Hodges et al., 1996, Hodges et al., 1992, Reilly et al., 2011a, Reilly et al., 2011c). The root cause of this associated anomia in AD remains highly controversial. One hypothesis is that patients experience a disconnection syndrome wherein impaired retrieval processes slow or prevent access to concepts (e.g., a patient might recognize a dog but fail to retrieve the name, dog). Conversely, others have argued that anomia in AD is the result of fundamentally
degraded semantic knowledge (e.g., patients are actively ‘forgetting’ what a dog is). There exist powerful arguments for both perspectives. Patients with AD do sometimes show preserved implicit knowledge of word meaning through priming (Rogers and Friedman, 2008). Yet, other researchers have shown that AD patients show a strong correlation between ‘naming and knowing’ such that semantic knowledge is more intact for objects that are successfully named relative to anomic items (Hodges et al., 1996, Hodges et al., 1992). In our own work, we have argued the basis for a dual locus of naming impairment in AD with roots both in degraded semantic content and in active retrieval processes that operate on such content (Reilly et al., 2011a).

Deficits in single word production carry forward and are amplified at the discourse level in AD. Narrative discourse in AD (e.g., tell me about your day) is characterized by a range of deficits, including diminished mean length of utterance, reduced syntactic complexity, ambiguous pronoun references (e.g., all characters are referred to as ‘it’), poor information content, and limited global cohesion (Gottschalk, 1994, Gottschalk et al., 1988).

In summary, the pathology of AD produces numerous linguistic disruptions, including anomia, alexia, and aphasia. Some of these language disorders (e.g., long sentence comprehension) arguably emerge secondary to primary memory impairment. Nevertheless, there exists a complex interaction between language and memory loss in AD that resists ‘clean’ root cause assessments. Moreover, variability both between and within patients with AD (e.g., some patients show priming effects, others do not) contribute to debate regarding why language disorders are present and how we might best intervene to ameliorate such problems.
Concluding Remarks

In this chapter, we have presented a necessarily highly selective review, merely scratching the surface of describing a small subset of dementias. This perspective was motivated both by space restrictions but also for a more dubious reason. That is, very little remains known about linguistic disruption associated with most non-Alzheimer’s dementia subtypes such as Vascular Dementia, Lewy Body Dementia, Parkinson’s Disease Dementia, Creutzfeld-Jacob Disease, HIV/AIDS Dementia Complex, and other mixed pathologies (Reilly et al., 2010). From an epidemiological standpoint, however, one aspect of dementia is now crystal clear. The changing demographics of aging throughout much of the industrialized world have made dementia a looming public health crisis.

Communicative impairments are among the most functionally debilitating symptoms of the dementias. Yet, we have only a rudimentary understanding of how to effectively treat the complex language impairments these patients experience. Moreover, treatment of dementia is not yet currently mandated as part of the curriculum for speech-language clinical programs in the USA, Australia, and the UK. Consequently, many practitioners apply techniques that may have efficacy for other populations (e.g., stroke aphasia) but have fundamental limitations in the context of a neurodegenerative condition. Thus, dementia presents a very new and pressing frontier for language rehabilitation research. Despite all of the unknowns regarding the potential for language rehabilitation in the dementias, several promising behavioral techniques have begun to emerge, including spaced retrieval training, errorless learning, group reminiscence
therapy, and Montessori-based skill learning approaches (Bier and Macoir, 2010, Jelcic et al., 2012, Savage et al., 2013 ahead of print).

Much like dementia diagnosis, the treatment of dementia can target a variety of either microscale (e.g., cellular) or macroscale (e.g. behavior) processes. Certainly, the optimal treatment for dementia would involve a “cure” that reverses tissue damage and restores neural function. Although this contingency seems unlikely, biomedical research has recently identified several recent protein targets and also developed agents that clear specific protein depositions (e.g., amyloid-b). Another approach involves prevention, through the development of vaccines that would be administered before dementia symptoms evolve. These vaccines would aim to prevent the cascade of microcellular damage associated with the neurodegeneration. Both of these approaches represent the future of dementia management. The present state of dementia treatment involves pharmacological agents that target the downstream effects of brain damage (e.g., depletion of acetylcholine) rather than slowing or reversing such damage. The philosophy of neurorehabilitation for the dementias has followed a parallel course. One argument is that cognitive rehabilitation should pursue compensatory approaches, modifying environmental cues and caregiver interactions to somewhat passively optimize a patient’s function. An alternative approach involves working directly with the patient to restore lost functions (e.g., retraining lost face-name associations).

In our own approach to the treatment of progressive language impairment we have embraced a middle ground between restoration and compensation of function. We argue that maintenance of extant cognitive function might prove more effective as a
treatment strategy for combatting language loss in a strategic way. Our treatment approach involves intensive semantic training and repeated naming of a small set of carefully crafted items (i.e., a microlexicon). This approach is unique in that it involves training a finite vocabulary and protecting a set of highly salient words against loss rather than retraining forgotten words ad hoc. This approach is also novel in that it forgoes treatment generalization in favor of functional naming of a highly constrained personal vocabulary.

In conclusion, the last decade has seen rapid advances in diagnostic specificity along with promising biomarkers that may eventually provide drug targets that slow or ultimately halt the progression of some forms of dementia. Yet, we have much to learn about cognitive-linguistic rehabilitation for the many millions of adults impacted by dementias. This complex societal problem will, therefore, require a multi-pronged attack coordinating prevention with evidence-based management of existing cases.

Acknowledgement

This work was funded by US Public Health Service grants DC010197 and DC013063 from the National Institute on Deafness and Other Communication Disorders.
References


2007. Clinical, genetic, and pathologic characteristics of patients with frontotemporal
dementia and progranulin mutations. Archives of Neurology, 64, 1148-53.
VERMA, M. & HOWARD, R. J. 2012. Semantic memory and language dysfunction in early
Experimental Psychology, 27, 635-657.
comprehension in patients with dementia of the Alzheimer’s type. Brain and language,
62, 361-397.
WILSON, S. M., HENRY, M. L., BESBRIS, M., OGar, J. M., DRONKERS, N. F., JARROLD,
W., MILLER, B. L. & GORNO-TEMPINI, M. L. 2010. Connected speech production in
three variants of primary progressive aphasia. Brain, 133, 2069-88.