Neurocase: The Neural Basis of Cognition

Primary Progressive Aphasia: A Review

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Primary Progressive Aphasia: A Review

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Abstract

This review summarizes clinical and imaging features associated with primary progressive aphasia (PPA). We investigate the hypothesis that these patients can be divided into subgroups of progressive non-fluent aphasia (PNFA) and semantic dementia (SD), based on their linguistic profiles and related imaging studies, and examine whether each of these major subgroups can be further subdivided. We focus on several critical features within each progressive aphasic subgroup. In PNFA, we examine agrammatism, phonologic disorder, and impaired verb processing to determine whether this syndrome is related to a modality-specific impairment in word formation and articulation, or a conceptual deficit that interferes with grammatical processing. In SD, we examine impaired semantic memory, limited remote memory, and anomia to assess whether this syndrome is due to a modality-neutral interruption of semantic memory, or the degradation of various material-specific representations of object features and words. We conclude that there is sufficiently consistent and converging evidence from clinical and imaging studies to support the claim that PNFA and SD are distinct subgroups of PPA. However, there does not appear to be sufficient evidence at this point to support further discrimination within these progressive aphasic subgroups. Testing hypotheses about finer-grained syndromes such as progressive dysarthria or progressive anomia has important consequences for improving our understanding of language organization and the neural basis for language.

Introduction

Primary Progressive Aphasia (PPA), a term coined by Mesulam (Mesulam, 1982), was first described by Arnold Pick about a century ago. In these path-breaking reports (Pick, 1892, 1901; translated by Girling and Berrios, 1994, 1997), Pick noted that speech was effortful but meaningful in one patient, while another patient had fluent but circumlocutory speech that was often empty. While Pick’s (Pick, 1892; translated by Girling and Berrios, 1994) first case also demonstrated a disorder of social comportment and personality, the impairment in other early cases was limited to language (Serieux, 1893; Rosenfeld, 1909). For example, Serieux’s case had progressive difficulty understanding single words beginning at 47 years of age, and this language deficit progressed over the subsequent 8 years.

Inspection of the brains of these patients revealed considerable focal atrophy, but no evidence for stroke, malignancy, head trauma, or other structural defect that could explain the language impairment. For example, Serieux’s case had significant bilateral temporal lobe atrophy (Dejerine and Serieux, 1897). Microscopic examination revealed loss of the large cortical pyramidal neurons. Several years later, Alzheimer and Altman also noted extensive neuronal drop-out, particularly in the superficial cortical layers, as well as other histopathologic changes in the atrophic frontal and temporal brain regions of Pick’s patients (Alzheimer, 1911; Altman, 1923). Thus, they described argyrophilic inclusions (Pick bodies) and swollen cells (Pick cells) as part of the pathologic picture of the condition that is often given the eponym “Pick’s disease” (Gans, 1922; Onari and Spatz, 1926).

More recently, Pick’s disease has been placed on a histopathologic continuum with several related conditions that have also been associated with PPA. For example, Constantinidis proposed a classification scheme for the various microscopic abnormalities associated with progressive aphasia (Constantinidis et al., 1974; Constantinidis, 1985; Tissot et al., 1985). He considered three conditions. All had evidence for neuronal drop-out, gliosis, and microvacuolation. Type A is the classic Pick’s disease with Pick bodies and swollen Pick cells. Type B includes only swollen cells, and today would probably be called Corticobasal degeneration (CBD). Type C of Constantinidis describes a pattern similar to Pick’s disease but without the intracytoplasmic inclusions or the swollen cells. These cases would now be labeled Dementia Lacking Distinctive Histopathology (DLDH) (Knopman et al., 1990; Giannakopoulos et al., 1995) or Frontotemporal Dementia of the Non-Alzheimer’s Type (Brun, 1987; Mann et al., 1993;
Neary et al., 1998). We now recognize that each of these diseases is due in part to distinct abnormalities in the metabolism of tau, a microtubule-associated protein coded on chromosome 17 (McKhann et al., 2001). Each of these histopathologic conditions has been associated with Primary Progressive Aphasia (Mann et al., 1993; Neary and Snowden, 1996; Turner et al., 1996; Lieberman et al., 1998; Kertesz et al., 2000), and indeed, other diseases such as Alzheimer’s disease (AD) (Greene et al., 1996; Galton et al., 2000) and ALS-dementia (Doran et al., 1995; Jackson et al., 1996) have been associated with PPA as well. Regardless of whether conditions such as Pick’s disease, CBD, and DLDH are thought to be variations of a single clinical-pathological entity or distinct conditions (Kertesz, 1997; Neary, 1997), the present review will focus on the clinical presentation of PPA.

It is not difficult to imagine that early descriptions of PPA challenged widely held views about dementia. Debate concerned whether a “focal” clinical presentation consisting primarily of aphasia, often unaccompanied by decline in cognitive domains such as memory, visual perceptual-spatial functioning, or executive difficulty, could properly be called “dementia” (Poeck and Luzzatti, 1988). Some investigators have contended that the language disturbance is merely the most obvious clinical manifestation in a patient with broad impairment in multiple cognitive domains, and that cases without reported non-linguistic deficits are due to limited ascertainment of non-language functioning (Poeck and Luzzatti, 1988; Green et al., 1990). A recent review has catalogued a surprisingly wide array of cognitive deficits in patients reported as having PPA (Zakzanis, 1999). The nosology of dementia from this perspective places PPA within a large spectrum of disease manifestations that includes classic dementia of the Alzheimer type as well as a range of other specific kinds of progressive cognitive limitation (De Renzi, 1986; Confavreux et al., 1992) and disorders of social comportment and disturbed personality (Snowden et al., 1996b).

Others have described cases of PPA that maintain relatively isolated aphasia until the terminal stages of the disease (Mesulam, 1982; Holland et al., 1985). These observations emphasize that true PPA involves no other cognitive impairment beyond language, and that PPA should be considered nosologically to be an independent entity (Mesulam, 2001). These investigators appropriately urge that caution should be exercised in interpreting abnormal results of neuropsychological tests in PPA, since many of these tests depend on linguistically-mediated instructions or verbal responses. We endorse Mesulam’s view that PPA presents with a dominant language disturbance that worsens gradually over time and is largely unaccompanied by other cognitive deficits for at least two years (Mesulam, 2001). However, other, non-linguistic components may play a role in the clinical presentation of PPA. For example, a disorder of working memory may contribute to various aspects of impaired language processing in PPA (Grossman et al., in press).

In the modern literature, awareness of PPA is due to Mesulam’s seminal description of five patients who presented with slowly progressive aphasia in the absence of classic features of dementia such as memory difficulty (Mesulam, 1982). The report described early deficits in word retrieval, but the patients subsequently differentiated themselves into two clinical subtypes. As in one of Pick’s initial cases, Mesulam described some cases with progressively effortful speech where utterances may have included single meaningful words. The other cases retained fluent speech that became increasingly circumlocutory and empty of content. Structural imaging with CT showed some atrophy in a left peri-Sylvian distribution. One of these patients was studied with positron emission tomography (PET) several years later (Chawluk et al., 1986). This showed reduced glucose metabolism in the left hemisphere. Other investigators have since described cases with fluent or non-fluent presentations of progressive aphasia, as well as cases showing mixed features (Snowden et al., 1989; Weintraub et al., 1990; Caselli and Jack, 1992; Hodges et al., 1992; Snowden et al., 1992; Karbe et al., 1993).

The potentially broad spectrum of linguistic presentation has sparked a debate about the nature of PPA: Do these patients represent a single entity with subtle clinical variations due to the evolution of the disease over time? Or do the fluent and non-fluent variants of PPA reflect distinct profiles determined by relatively unique patterns of neuroanatomic involvement? In the review that follows below, we explore whether patients can be categorized as non-fluent or fluent, fully acknowledging that there are patients with progressive mixed aphasia who present with elements of both non-fluent and fluent aphasia. In each group of progressive aphasics, we will present an overview of the clinical presentation, and then focus on several key issues associated with the condition. We will also discuss the imaging data associated with each condition. We will use these observations to highlight the key features that differentiate fluent from non-fluent forms of progressive aphasia. Moreover, we consider further subcategorizations that have been proposed within each major progressive aphasic subgroup, and examine hypotheses about the sources of these syndromes that are entailed by these fine-grained subgroupings. In the non-fluent form of progressive aphasia, we focus on competing accounts of their non-fluent speech: Is this due to a modality-specific deficit that interferes with phonologic assembly and articulation? or a conceptual deficit at the level of grammatical processing of single words and sentences? In the fluent form of progressive aphasia, we evaluate competing claims about impaired semantic memory: Is this due to the degradation of various modality-specific forms of knowledge such as visual-perceptual features of objects and phonologic representations of words? or to a modality-neutral deficit in semantic memory that interferes with the comprehension of a concept in any of its possible manifestations? To anticipate our conclusion, we believe that there is sufficient evidence to support the subcategorization of PPA into non-fluent and fluent variants. While each of these clinical subgroups is by no means homogeneous, we do not believe that there are sufficient data at present to support further subcategorization of these patients into conditions.
such as “progressive dysarthria” or “progressive anomia”. This view is based largely on cross-sectional observations that define the aphasic characteristics of PPA patients, on longitudinal data that demonstrate sustained clinical distinctions between the fluent and non-fluent variants of PPA over time, and on imaging data that associate progressive non-fluent aphasia (PNFA) and semantic dementia (SD) with different neuroanatomic distributions of disease. We argue that additional imaging studies are needed in comprehensively characterized patients to examine whether variations of a syndrome’s presentation are due to a single neural mechanism or to disease compromising adjacent brain regions that subserve different functions.

**Progressive non-fluent aphasia**

Arnold Pick’s early clinical description of this condition included a woman whose speech became progressively effortful and eventually led to complete muteness (Pick, 1892; Girling and Berrios, 1994). Several of the patients described more recently by Mesulam had progressive loss of speech output and impaired repetition, despite relatively preserved aural comprehension of single words (Mesulam, 1982). Many studies have since described impairments in speech production. Some of these PNFA patients were most notable for their distorted speech (Kartsounis et al., 1991; Tyrrell et al., 1991). Paraphasic errors, often evident in spontaneous speech and repetition, were more frequently phonemic rather than semantic (Crook et al., 1998). These findings are consistent with the hypothesis that PNFA is fundamentally a modality-specific disorder of speech and articulation, possibly related to degraded phonologic representations of words. Other investigators have attributed the effortful and agrammatic speech of PNFA patients to a deficit at a central level of grammatical processing that also causes comprehension difficulty (Snowden et al., 1992; Grossman et al., 1996; Hodges and Patterson, 1996; Thompson et al., 1997). We focus below on three features of language in PNFA that highlight this controversy: Agrammatism, dysarthria, and naming difficulty.

**Agrammatism**

Agrammatism refers to speech that is effortful, dysprosodic, and slow, associated with the omission of free and affixed grammatical morphemes from sentences. Oftentimes sentence comprehension is impaired, although single word comprehension is relatively preserved. Several cases of PNFA have been described in the literature with this presentation. For example, one of Tyrrell’s subjects presented with impaired sentence construction and naming difficulty (Tyrrell et al., 1990). Speech became progressively limited, with utterances becoming shortened to single words and ultimately limited to grunting. Case 2 of Kempler had difficulty understanding sentences (Kempler et al., 1990). Caselli described three patients with non-fluent speech, phonemic paraphasic errors, and impaired sentence repetition (Caselli and Jack, 1992). Performance was impaired on the Token Test, a measure requiring comprehension of complex instructions to manipulate colored geometric shapes.

Longitudinal studies have provided rare but extraordinarily valuable confirmation of the sentence processing deficit in PNFA. For example, a careful analysis of discourse speech samples revealed important characteristics of impaired sentence expression in PNFA patients studied longitudinally (Thompson et al., 1997). These patients became increasingly non-fluent over time, and the clarity of their speech declined. Mean length of utterance was significantly shortened in three of the four patients, and this was associated with agrammatic sentence production and limited sentence repetition. These patients also showed declining sentence comprehension. Another report described the longitudinal course of three PNFA patients (Weintraub et al., 1990). Speech fluency gradually declined, containing increasing numbers of grammatical errors and phonemic paraphasic substitutions. Speech clarity also declined, and the patients ultimately became mute, although they continued to be independent in their activities of daily living. The patients also exhibited an unrelenting decline on measures such as the Token Test, repetition (particularly for sentences), and the Boston Naming Test. Decline on measures of buccofacial praxis and reading was relatively modest, and performance was stable over time on measures such as orientation, design recall, line orientation, face recognition, and Raven’s Progressive Matrices. A report described the longitudinal course of 10 primary progressive aphasics on the Western Aphasia Battery (Karbe et al., 1993). Speech fluency and oral expression declined together with repetition and confrontation naming. Two PNFA patients were examined longitudinally on a wide variety of language and cognitive measures (Hodges and Patterson, 1996). Impairments were seen on measures of sentence comprehension and sentence-picture matching that require an appreciation of grammatical relationships in sentences, as well as modest difficulty on measures of confrontation naming, repetition, and phoneme discrimination. Their comprehension of single words on word-picture matching tasks was relatively preserved. A longitudinal characterization of four PNFA patients was provided in comparison to 25 patients with Alzheimer’s disease (Grossman et al., 1996). The speech of the PNFA patients became progressively less fluent. Their naming and repetition declined over several years. Comprehension of sentences involving grammatical elements also decayed throughout the disease process, while comprehension of single words declined only late in the patients’ course.

Some researchers have begun to investigate the basis for the language deficit in PNFA. The critical feature in many of these patients appears to be a grammatical impairment that interferes with fluent expression. This should be distinguished from SD patients whose speech may appear non-fluent at times due to frequent word-finding pauses, and from FTD patients with limited executive functioning who have reduced fluency due to an apathetic, amotivational state. While PNFA patients often have distorted spontaneous speech, many PNFA...
patients have grammatical comprehension difficulty in sentences as well, suggesting that the deficit cannot be attributed entirely to a disorder of articulation and motor aspects of speech. For example, two cases of PNFA described by Hodges and Patterson (1996) had progressive decline on the Test of Reception of Grammar (TROG), a measure of sentence-picture matching that involves manipulations of number, location, and phrase structure in sentences. Thompson and her co-workers (Thompson et al., 1997) reported declining comprehension in several PNFA patients on Part V of the Token test that requires interpretation of complex relational terms in aurally-presented sentences. In another report, four PNFA patients were shown to be impaired in their comprehension of grammatically complex sentences with subordinate clauses compared to grammatically simple sentences on measures of sentence-picture matching and responding to oral probes of sentences (Grossman et al., 1996). A parallel expressive deficit was seen on a sentence completion task, where the PNFA patients encountered considerable difficulty describing pictures that require grammatical phrasing such as the passive voice. Observations of concurrent difficulty on measures of grammatical expression and grammatical comprehension suggest that declining fluency in PNFA is due in part to an impairment of grammatical processing at a central level concerned with the appreciation of sentence structure.

Perhaps the most convincing evidence for a grammatical processing deficit in PNFA comes from detailed experimental studies of grammatical comprehension (Tyler et al., 1997; Grossman et al., in press). These investigators reported impairments during off-line assessments of syntax in sentences. One of these studies also noted a correlation between impaired grammatical comprehension and limited working memory, suggesting a role for limited executive resources in the sentence comprehension impairments of PNFA patients (Grossman et al., in press). To minimize the interpretive confound associated with the executive and working memory demands of off-line sentence comprehension assessments, these investigators also administered an “on-line” measure of grammatical processing with a word monitoring technique. This method requires subjects to indicate when they hear a target word in a sentence. Unbeknownst to subjects, the target word immediately follows a grammatical agreement. When the grammatical agreement contains an error, healthy control subjects show a brief delay in their response to the target word relative to the condition where the target word follows a correct grammatical agreement. This effect is not seen when the target word is presented outside of the temporal processing envelope of the grammatical agreement, that is, several words after the grammatical agreement. Using this on-line technique, both studies demonstrated insensitivity to several kinds of grammatical relationships in sentences (Tyler et al., 1997; Grossman et al., in press). One of these reports also described sensitivity to the grammatical agreement following a delay that is beyond the temporal window of normal grammatical processing (Grossman et al., in press). The authors speculated that sentence information held in auditory-verbal working memory during sentence processing becomes degraded while grammatical agreement knowledge is activated over an abnormally slowed time course. Thus, in addition to a deficit in speech that has many agrammatic characteristics, many PNFA patients also have sentence comprehension difficulty. Some work suggests that this may not be due to the degradation of grammatical knowledge, but instead appears to be related to some aspect of grammatical knowledge, such as the executive resources supporting long-distance syntactically-dependent relationships in sentences.

**Dysarthria**

Yet others attribute non-fluent speech in PNFA to a modality-specific deficit expressing phonologic properties of words (Kartsonis et al., 1991; Croft et al., 1998). This can be manifested clinically as dysarthria or phonemic paraphasic errors. A prominent feature of one of Kempler’s three progressive agrammatic patients (Case 2) was slow, dysprosodic, and hypophonic speech production (Kempler et al., 1990). Delecluse and her co-workers described a patient with impaired spontaneous speech due to compromised fluency, dysprosodia, and impaired articulation (Delecluse et al., 1990). Three PNFA patients have been described with prominent phonemic paraphasic errors (Caselli and Jack, 1992). Another patient showed progressively reduced speech output that was effortful, halting, and poorly articulated, associated with orofacial dyspraxia as well as limb apraxia (Tyrrell et al., 1991).

Thompson and her co-workers (Thompson et al., 1997) have been among the few to quantify the speech disorder of PNFA patients. Using the scoring system of the Boston Diagnostic Aphasia Examination, they observed progressive loss of articulatory agility and melodic line in four PNFA patients. They also observed progressively slowing speech rate and prolonged pauses in an all four patients, while reduced speech intelligibility was found in two of the patients. A detailed study of language production in two PNFA patients found relatively greater difficulty on naming compared to reading and repetition (Croft et al., 1998). This was attributed to the minimal phonologic support provided by the naming task. Consistent with a phonologically-based account of limited speech output, these investigators also noted a word length effect, where greater difficulty producing long words was attributed to the increased opportunity to produce an error. Thus, in contrast to much of the work investigating sentence processing difficulty in PNFA, other studies of PNFA have emphasized that their non-fluent speech is due to a modality-specific disorder of speech processing, possibly at the level of the phonologic representation of a word, that results in dysarthria.

**Naming**

The controversy surrounding the source of non-fluent speech in PNFA is underlined by studies of their naming difficulty. Mesulam observed that most PPA patients – including patients with PNFA – present with word-finding problems (Mesulam,
Examinations of spontaneous speech in PNFA are consistent with the observation of impaired word-finding, and this difficulty seems to progress during the course of the illness (Weintraub et al., 1990; Grossman et al., 1996; Hodges and Patterson, 1996; Thompson et al., 1997). In a study of 25 PNFA patients, 24% of individual patients had a statistically significant confrontation naming impairment early in the course of their disease (Moore et al., 2003). A correlation analysis associated their difficulty with a limitation in lexical retrieval and related downstream processes such as lexical phonologic assembly. A systematic analysis of errors during performance of a confrontation naming task found phonemic paraphasic substitutions and omissions, paralleling their spontaneous speech (Weintraub et al., 1990). These observations imply a naming deficit in PNFA at the level of phonetic assembly of a word form. Evidence consistent with a modality-specific deficit at the level of a word form comes from frequent observations of a modality-specific effect in PNFA expression, with greater difficulty speaking than writing in longitudinal studies (Weintraub et al., 1990; Grossman et al., 1996).

Most of the work described above was concerned with the production of nouns. Verb naming difficulty has been reported in FTD (Cappa et al., 1998), and more recently in patients with PNFA (Hillis et al., 2002). However, the basis for a deficit with verbs is unclear. One report has emphasized a modality-specific effect in verb naming in PNFA, pointing out the preferential deficit in oral naming relative to written naming (Hillis et al., 2002). These investigators observed semantic paraphasic substitutions during verb naming errors, such as the production of associated object names, in contrast to the phonemic paraphasic errors in PNFA noun naming and spontaneous speech noted by others. These observations of verb naming difficulty were thought to be most consistent with a modality-specific deficit at the level of a word form for a specific lexical category.

However, other evidence appears to be more consistent with a verb processing deficit at a conceptual level. For example, PNFA patients showed verb comprehension difficulty on a word-picture matching task (Rhee et al., 2001). Difficulty producing action verbs has been correlated specifically with the histopathologic distribution of disease in motor association cortex in PNFA patients who have motor neuron disease (Bak and Hodges, 1999; Bak et al., 2001). The authors attributed action verb naming difficulty to the degradation of sensory-motor semantic features associated with this class of verbs that are stored in motor association cortex. Moreover, verbs play a critical role in structuring sentences, such as organizing the structure (must a verb take a direct object?) and the thematic roles (who does what to whom) of a sentence. A deficit at a central level of verb processing implied by these observations has been linked to PNFA patients’ impaired sentence processing. Investigators thus have noted verb production difficulty in association with shortened utterance length and agrammatic sentence structure in discourse speech samples of PNFA patients (Thompson et al., 1997). In three of the four reported patients, the ratio of verbs to nouns in spontaneous speech was considerably decreased. When verbs were produced, these investigators observed verbs with simplified or incorrect morphology, and verbs were associated with incorrect argument structure. Findings such as these emphasize the possibility that a conceptual deficit involving degraded verb knowledge may also contribute to limited sentence processing and non-fluent speech in PNFA.

Taken together, these observations suggest that several factors may contribute to the effortful and non-fluent speech pattern in PNFA. Among these are an impairment at a conceptual level that interferes with grammatical processing, and a modality-specific deficit that results in poor control over the phonologic properties of speech. While some PNFA patients demonstrate both a grammatical impairment interfering with sentence comprehension and dysarthric speech, it is important to note that we also observe dissociations between these features. This includes patients with pure dysarthria but no agrammatism, or patients with obviously agrammatic comprehension and production that is clearly articulated. While cognitive dissociations such as these allow us to hypothesize that PNFA is a syndrome comprised of several linguistic features, reports of patients with comprehensive characterizations of performance in all of the relevant domains are rare. Additional work is needed to achieve a fair determination of the basis for non-fluent speech in PNFA.

These competing accounts also can be addressed through converging evidence from other sources. One such source involves imaging. Modern neuroimaging techniques are able to obtain an in vivo representation of the brain of a PNFA patient with high spatial resolution that can test hypotheses regarding the structurally and functionally distinct neural substrate of each of these linguistic features.

**Neuroimaging features of PNFA**

Quantitative structural imaging has been rare in PNFA. Mesulam suggests that atrophy is diffuse, spread throughout the Sylvian fissure of the left hemisphere (Mesulam, 2001). However, a specific pattern of reduced cortical activity appears to be emerging in neuroimaging studies of patients specifically with PNFA. This includes a deficit in the inferior and dorsolateral prefrontal regions extending into the anterior-superior temporal area of the left hemisphere. A PET scan of Kempler’s PNFA patient (Case 2) revealed hypometabolism in left frontal regions that extended into adjacent superior temporal and inferior parietal regions (Kempler et al., 1990). The PET scans of Tyrrell’s PNFA patients also showed defects in left frontal and superior temporal regions (Tyrrell et al., 1990). In the three PNFA patients described by Caselli, left frontal atrophy was seen on MRI, and SPECT scans demonstrated hypoperfusion centered in the left frontal region (Caselli and Jack, 1992). A quantitative study of two PNFA patients using voxel-based morphometric analyses of MRI revealed two distinct patterns of cortical atrophy: One revealed predominantly frontal atrophy, and a second showed posterolateral...
temporal atrophy (Rosen et al., 2002). A longitudinal pattern of non-fluent language impairment seen in four PNFA patients was associated with a PET defect in the middle frontal, inferior frontal, and anterior-superior temporal regions of the left hemisphere (Grossman et al., 1996).

It is unreasonable to infer a brain-behavior relationship only on the basis of a neuroanatomic defect since PNFA patients have many cognitive deficits. The mere presence of a neuroanatomically defined defect does not help determine whether this is related to a grammatical processing impairment or a modality-specific disorder in phonologic assembly and articulation. The relationship between a left frontal cortical defect and impaired sentence comprehension has been studied quantitatively by directly correlating cognitive performance with SPECT (Grossman et al., 1998) or arterial spin labeling MRI (Alsup et al., 2000) in FTD. A significant correlation between impaired grammatical comprehension and reduced dorsolateral and inferior frontal activity was found. A quantitative assessment of cortical atrophy in 7 PNFA patients with voxel-based morphometric analyses of structural MRI demonstrated a correlation between left inferior frontal atrophy and impaired comprehension of grammatically complex sentences (DeVita et al., 2002). Moreover, the correlation of left inferior frontal atrophy was significantly greater for grammatical comprehension than working memory. Unfortunately, these studies did not examine speech deficits concurrently in these patients.

Analysis of the neural activation pattern monitored by BOLD fMRI during a sentence comprehension experiment has provided additional evidence associating a grammatical deficit with left inferior frontal disease in PNFA (Cooke et al., 2003). Three PNFA patients read grammatically complex sentences such as “The boy that Amy chased was friendly”. These contained an object-relative center-embedded subordinate clause (italicized) and a lengthy linkage between the head noun phrase and the point where it is interpreted in the subordinate clause (underlined). The PNFA patients had difficulty understanding the object-relative sentences, although their performance was not degraded by the elongated linkage between the two relevant portions of the sentence. During comprehension of these sentences, healthy control subjects recruited ventral portions of left inferior frontal cortex (Brodmann area 45/47) that appear to be related to grammatical aspects of sentences, and dorsal portions of left inferior frontal cortex (Brodmann area 44/6) that are associated with verbal working memory. PNFA patients failed to show significant activation of the left ventral inferior frontal region during attempts to understand these grammatically-demanding sentences, although they were able to activate the dorsal portion of left inferior frontal cortex. This suggested that the PNFA patients have particular difficulty with grammatical aspects of sentence comprehension due to FTD had difficulty understanding the sentences with a long intra-sentential linkage, although their performance was not degraded by a grammatically-complex, object-relative, center-embedded clause. These patients were able to activate ventral portions of left inferior frontal cortex, but did not recruit dorsal portions of left inferior frontal cortex associated with verbal working memory.

Despite these demonstrations of a relationship between grammatical aspects of sentence comprehension and ventral portions of left inferior frontal cortex, it remains difficult to assert with confidence that a defect in left inferior frontal cortex functioning is specific for a grammatical impairment. Most of the work relating left inferior frontal cortex to grammatical aspects of sentence comprehension is correlative in nature, for example, and the three PNFA patients studied in the BOLD fMRI experiment of sentence comprehension were not dysarthric. Perhaps more importantly, imaging studies in patients with dysarthric speech also have shown a left frontal defect (Kartsounis et al., 1991; Tyrrell, Kartsounis et al., 1991). Relatedly, a correlational study using voxel-based morphometric analyses of MRI examined the neural basis for difficulty naming nouns orally in PNFA (Grossman et al., 2004). This work demonstrated a correlation between the component of naming involving lexical retrieval and downstream processes such as phonologic assembly and cortical atrophy in a neuroanatomic distribution that includes left inferior frontal cortex. This study implies an association between a modality-specific speech deficit and left inferior frontal cortex in PNFA that is quite similar in its distribution to the neuroanatomic locus associated with grammatical difficulties in PNFA. Direct contrasts of imaging studies comparing PNFA patients with a pure agrammatic impairment and patients purely dysarthric speech have not been performed to determine whether the compromised regions in these PNFA subgroups are dissociable.

Taken together, these observations suggest a core deficit in PNFA consisting of effortful, non-fluent speech. Many of these patients appear to have an impairment in sentence expression and comprehension. This may be related in part to factors such as a deficit processing grammatical aspects of sentences. Other patients appear to have impoverished phonologic representations of words that results in dysarthric speech and phonemic paraphasic errors. This evidence raises the possibility that PNFA may include two dissociable, non-fluent aphasic syndromes – a conceptual deficit that includes impaired grammatical comprehension, and a modality-specific deficit that produces dysarthria. However, the evidence does not appear to be strong enough at present to rule out a single underlying cause of these difficulties. Converging evidence from neuroimaging findings suggests that compromised left inferior frontal cortex plays a crucial role in the impaired language profile of PNFA patients. The most compelling work relates an impairment of grammatical comprehension to limited left inferior frontal functioning, although left frontal disease also appears to be associated with modality-specific word forms and dysarthria. In the absence
of direct comparisons between PNFA subgroups, we cannot
determine whether two adjacent regions in left inferior frontal
cortex support grammatical processing and modality-specific
speech production. Additional neuroimaging work in com-
prehensively characterized patients is needed to establish
whether clinical components of the progressive non-fluent
profile are dissociable into anatomically distinct subregions
that support separate conceptual and modality-specific fea-
tures of language in PNFA.

Semantic dementia
Another form of progressive aphasia has been described that
is quite different from the non-fluent aphasic syndrome
depicted above. Pick described three cases of progressive
fluent aphasia associated with atrophy of inferior regions of
the temporal lobe (Pick, 1904; Girling and Berrios, 1997). A
contemporary of Arnold Pick, Max Rosenfeld, also provided
an early description of a patient with word-finding difficulty,
including a striking loss of the names of objects, and cir-
cumlocutions and semantic paraphasic errors in spontaneous
speech (Rosenfeld, 1909; Luzzatti and Poeck, 1991). These
patients are said to have a fluent form of progressive aphasia,
also known as semantic dementia (SD) (Snowden et al.,
1989).

Modern descriptions of SD were first provided by
Warrington, who reported three patients with impaired seman-
tic memory (Warrington, 1975). These patients had circum-
locutory spontaneous speech with frequent paraphasias.
Speech was at times empty of meaningful content. The
patients had difficulty on language expression tasks depen-
dent on semantic memory such as defining words and
confrontation naming. Their comprehension of single words
also was impaired, associated with impoverished knowledge
of the semantic features linked to words. The central, seman-
tically-based nature of these deficits was emphasized by
two additional observations: They had difficulty in other
modalities of stimulus presentation such as recognizing
visually-represented objects, despite minimal deficits in
visual perception; and their semantic memory impairment
disproportionately affected a specific category of knowledge
(natural kinds such as animals) compared to other categories
(manufactured artifacts such as tools). Surface dyslexia and
surface dysgraphia were present, often associated with reg-
ularization errors. However, other aspects of language such as
syntax and repetition appeared to be preserved.

Many investigators have since described patients with SD.
Controversy nevertheless persists about the basis for the
semantic memory deficit in these patients. One account
attributes their semantic memory difficulty to a central,
modality-neutral impairment that compromises the meaning
of a concept regardless of the material or modality used for its
presentation. An alternate account suggests that the semantic
memory deficit is due to the degradation of modality-specific
representations, such as degraded visual-perceptual feature
knowledge of objects represented in modality-specific visual
association cortex, and degraded phonologic representations of
words that impairs their naming, reading, and writing. In our
discussion of SD, we focus on the basis for their impaired
semantic memory, and some possible consequences of their
semantic memory deficit, namely, difficulty reading and writing
irregularly spelled words and a remote memory impairment.

Semantic memory
Several studies have been conducted to investigate the basis for
the semantic memory impairment in SD. One view attributes
the semantic memory deficit in SD to a modality-neutral
impairment for any aspect of knowledge represented in seman-
tic memory. Warrington emphasized a limitation in semantic
memory across multiple modalities of stimulus presentation
(Warrington, 1975). In addition to deficits on visually-mediated
measures dependent on semantic memory such as sorting
pictured objects based on characteristic features, and anomaly
judgments of visually-presented chimeric combinations of two
objects (Hodges and Patterson, 1996; Hodges et al., 1999), SD
patients also were impaired on language-mediated deficits for
associative knowledge. Hodges and his co-workers also
demonstrated that SD patients have relatively poor associative
knowledge of non-visual features related to the meaning of
names of natural kinds (e.g. impoverished knowledge of
whether a deer is domestic or gives milk), despite relatively
preserved superordinate knowledge (e.g. they know that a deer
is a kind of animal) (Hodges et al., 1992, 1995). One study has
demonstrated SD patients’ impairment judging the meaning of
auditory representations of objects (Bozeat et al., 2000). Patients
with SD also have difficulty demonstrating the use of
objects when their knowledge of the object’s meaning is
degraded (Hodges et al., 2000; Bozeat et al., 2002b). It is
interesting in this context that SD patients are more accurate
in the use of personal instances of an object relative to other
eamples of the same object that do not belong to the patient
(Bozeat et al., 2002a). These observations suggest that a
modality-neutral semantic memory deficit compromises all
forms of knowledge associated with a concept.

An alternate approach is based largely on the observation of
category-specific impairments for particular domains of
knowledge. Thus, it appears that some SD patients have a
“reversal of the concreteness effect”, where there is relative
difficulty with concrete objects compared to abstract concepts
(Warrington, 1975; Breedin et al., 1995; Cipolotti and
Warrington, 1995; Snowden, 1999). Additional support for the
selective degradation of visual-perceptual features of
object-related knowledge in semantic memory comes from
SD patients’ relatively preserved number knowledge compared
to their impaired knowledge of objects (Diesfeldt, 1993;
Cappelletti et al., 2001; Halpern et al., in press). More detailed
assessments of SD have emphasized a relative deficit within
object categories for natural kinds compared to manufactured
artifacts (Warrington, 1975; Basso et al., 1988; Tyrrell et al.,
1990; Cardebat et al., 1996). An impairment for natural
kinds has been associated with the relative degradation of
visual-perceptual features that are hypothesized to be particularly important for categories like natural kinds relative to manufactured artifacts (Warrington, 1975). Observations such as these seem most consistent with the claim that semantic memory deficits in SD are due in part to the modality-specific degradation of visual-perceptual feature knowledge.

A critical evaluation of category-specific effects raises questions about the status of feature knowledge and the modality-specific nature of the semantic memory deficit in SD. For example, some investigators have pointed out disturbing inconsistencies in the category-specific semantic memory difficulties across individual cases (McRae et al., 1997; Caramazza and Shelton, 1998; Tyler et al., 2000). Category-specific difficulty for natural kinds without preferential degradation of perceptual features also has been described (Funnell and De Mornay Davies, 1992; Lambon Ralph et al., 1998; Moss et al., 1998; Samson et al., 1998). Across these individual cases, dissociations within categories of knowledge as broad as natural kinds are apparent as well, raising concerns about the coherence of such a large category that indiscriminately depends on a particular kind of feature. Some investigators thus observed greater difficulty with animals than fruits and vegetables (Hart and Gordon, 1992; Caramazza and Shelton, 1998), while others found the reverse (Hart et al., 1985; Farah and Wallace, 1992). Moreover, a recent patient with SD was reported to have more difficulty with manufactured artifacts than natural kinds (Biran et al., 2002). We have observed these kinds of category-specific dissociations in individual SD patients for both natural kind and manufactured artifact subcategories on a confrontation naming task. At another level, the status of visual-perceptual features and associative knowledge related to the target concepts has been poorly specified. Some features thus appear to be necessary (e.g. a deer is a mammal, so it must give milk), while other features are characteristic and not at all necessary (e.g. there is nothing that necessarily restricts a deer’s geographic habitat within a moderate climate). It is the former, relatively necessary type of feature that would appear to be more critical for the meaning of a concept, and it is unclear whether this type of feature is particularly compromised in SD. Moreover, not all visual-perceptual feature knowledge is compromised in SD: SD patients appear to show relative preservation of color knowledge (Robinson and Cipolotti, 2001). Thus, semantic memory deficits in SD do not appear to be explained easily by modality-specific accounts of degraded visual-perceptual feature knowledge.

Additional evidence for a modality-neutral effect comes from a series of studies examining the nature of impaired semantic memory in SD from the perspective of the processes involved in integrating a set of features into a coherent concept for the purpose of semantic categorization. One of these categorization processes is similarity-based, since it involves an overall perceptual comparison of a test object with a prototype or previously encountered exemplars of a target category. A second process is rule-based, involving selective attention to features critical to category membership, inhibitory control over incidental features, and maintenance of these feature sets in working memory until an object’s category membership can be determined. In one series of experiments, patients were asked to judge whether a brief verbal object description (e.g. “a round object 3 inches in diameter”) is a member of one of two familiar categories (e.g. PIZZA or QUARTER) (Grossman et al., in press). Note that the description cannot belong to one of the categories: A quarter is not 3 inches in diameter by definition. These decisions were presented under two instruction conditions: A similarity-based condition, or a rule-based condition. Under the rule-based condition, control subjects noted that a quarter is not 3 inches in diameter, and therefore categorized the described object as a pizza. During the similarity-based condition, the subjects noted that the diameter of the described object is roughly half-way between the two categories, and control subjects accordingly judged the described object to be a member of each category equally often. Control subjects thus shifted their categorization decisions under similarity-based instructions, demonstrating their ability to engage either semantic categorization process. By comparison, FTD patients were able to use only similarity-based processing to make category membership decisions, regardless of the instruction condition. They thought that a three-inch round object is a QUARTER or a PIZZA equally often. To demonstrate that patients had preserved sensitivity to feature knowledge and were not simply responding randomly, enriched object descriptions were also presented. These included an additional, non-necessary feature (e.g. “a round object 3 inches in diameter found in arcades”). The incidental feature was always associated more strongly with the object possessing the constrained feature – in this case, QUARTER. Control subjects and FTD patients both demonstrated their sensitivity to this non-necessary feature in their judgments by biasing their categorization decisions toward the category associated with “arcades”. A comparison of FTD subgroups failed to demonstrate any differences between PNFA patients, SD patients, and non-aphasic patients in this study. These findings were thought to be most consistent with the claim that semantic memory impairments in FTD – including patients with SD – are due in part to a limitation in the semantic categorization processes that integrate features into a coherent concept.

In a second study, the authors evaluated the possibility that SD patients’ semantic categorization performance was impaired in the previous experiment because rule-based decisions depended on knowledge acquired remotely that may have been degraded. For example, degraded feature knowledge may have compromised SD patients’ knowledge of the diameter of a quarter. Patients were taught a new visual category – a novel, natural-appearing animal – under rule-based or similarity-based categorization conditions (Koenig et al., 2003). During category acquisition based on a rule, subjects were shown a set of 4 critical features and given a rule – in this case, that a category member must have 3 of the 4 critical features. At the same time, they were shown two
stimuli, and were asked to decide which of the two stimuli is a category member. During similarity-based category acquisition, patients were shown a prototype member of the category and two stimuli, and were asked to decide which of the two stimuli is a category member based on the overall perceptual similarity of a stimulus to the prototype. During the subsequent test phase, subjects were shown 64 stimuli one at a time and asked to decide whether each is a member of the category. Control subjects who were taught the category in a rule-based manner showed a category-like effect that distinguished sharply between members (possessing 3 or more critical features) and non-members (possessing fewer than 3 critical features). Following similarity-based training, however, control subjects showed graded category membership decisions that reflected the number of features in the test stimulus shared with the prototype. This again demonstrated the flexibility that control subjects possess in their ability to implement either rule-based or similarity-based semantic categorization processes. SD patients’ performance resembled control subjects. They showed a category-like effect during rule-based categorization, and graded decisions based on the number of features shared with the prototype during similarity-based categorization. PNFA patients and non-aphasic FTD patients with an executive deficit showed only graded category membership decisions, regardless of the training condition. These findings emphasize that SD patients are able to use semantic categorization processes to integrate features into a coherent concept, including visual-perceptual features, when decisions do not depend on previously acquired knowledge represented in semantic memory. Observations such as these are most consistent with the hypothesis that SD patients’ semantic memory deficits are related to the degradation of material-neutral feature knowledge.

SD patients also have impaired confrontation naming. Confrontation naming requires a semantic component, and limited semantic activation may contribute to impaired naming in SD. This conclusion is based on an analysis of naming errors that shows frequent contrast coordinate and superordinate semantic substitutions, and the occurrence of substitutions with decreasing meaningfulness as the semantic impairment worsens in longitudinal studies of SD (Hodges et al., 1995; Lambon Ralph et al., 2001). Despite visual-perceptual deficits in some patients with FTD (Pachana et al., 1996; Boone et al., 1999; Razani et al., 2001; Glosser et al., 2002), a visual-perceptual deficit alone is unlikely to explain fully the confrontation naming difficulty in SD because these patients are also impaired at naming to a verbal description of an object.

An alternate account attributes the naming difficulty in SD to the modality-specific degradation of lexical phonological representations, or to poor access to lexical phonological representations from semantic memory. Some patients are said to have progressive anoma, with profound naming difficulty but relatively preserved semantic memory. One well-studied patient showed a disproportionate deficit with low frequency target words, consistent with the limited retrieval of phonological representations of words (Graham et al., 1995). It is also possible to suggest a dual basis for naming difficulty in SD. A naming deficit in some SD patients may be due to a phonologically-based impairment, while a naming deficit in other SD patients may be attributable to degraded semantics. However, this dual account of naming difficulty in SD has been questioned from several perspectives. First, Lambon Ralph and his colleagues have modeled confrontation naming and semantic memory difficulty in SD with a constraint-satisfaction approach (Lambon Ralph et al., 2001). They showed that a single semantic deficit can explain both progressive anoma and semantic memory deficits. Second, the high intercorrelations between properties of words such as frequency (more often associated with retrieval) and familiarity (more often associated with semantic representations) makes it difficult to dissociate the material-specific lexical phonological account and the material-neutral semantic account of naming difficulty in SD based solely on these properties of words. Relating independent measures of semantic memory and lexical retrieval to confrontation naming through correlation and regression analyses generally has been hampered by the assessment of smaller groups of SD patients. One study has investigated the relationship between confrontation naming and independent measures of lexical retrieval, semantic memory, and visual-perceptual functioning in a large group of SD patients (n = 26) (Moore et al., 2003). This work confirmed a significant naming deficit in 61% of individual SD patients when first seen. Even mildly demented SD patients were significantly impaired at the onset of disease, and the deficit was significantly worse in SD than in PNFA throughout the mild and moderate stages of the disease. Correlation and regression analyses associated the naming impairment with impaired lexical retrieval and degraded semantic memory representations. Our impression is that SD often presents with a significant naming deficit that is reminiscent of so-called progressive anoma. However, most of these patients develop a semantic impairment when followed longitudinally, as suggested by Lambon Ralph and his associates (Lambon Ralph et al., 2001).

In sum, these findings are consistent with the hypothesis that SD patients have impairments on tasks involving semantic memory. However, the impairment does not appear to compromise all conceptual domains equally, affecting knowledge associated with objects more than number knowledge or knowledge of abstract concepts. Some argue that impairments on semantic memory tasks in SD are due in large part to a modality-specific deficit, such as degraded knowledge of visual-perceptual features or phonologic representations. Many observations suggest instead that the semantic memory deficit in SD is related to a modality-neutral deficit in object knowledge. Thus, multiple representations of objects – including auditory and action representations – appear to suffer in SD.

One way to establish the nature of impaired semantic memory in SD is through converging evidence obtained from neuroimaging studies. This approach can examine the
relationship between impaired semantic memory and the neural substrate for SD with correlative studies of cognitive performance and regional cortical atrophy. One goal may be to determine whether dissociable but adjacent brain regions subserve modality-specific representations of object features and lexical phonologic representations rather than a single, modality-neutral semantic memory mechanism.

**Remote memory**

Impaired semantic memory in SD appears to have significant consequences for other forms of memory as well (Murre et al., 2001). Assessments of autobiographical memory have revealed that SD patients have relatively better recall of recent events than remote events, although they are impaired at recalling all time intervals (Snowden et al., 1996a; Graham and Hodges, 1997; Graham et al., 1997; Graham et al., 1998; Graham et al., 1999). SD patients also appear to demonstrate the same gradient (recent events recalled more accurately than remote events) for non-personal, factual events, although these do not appear to be recalled as accurately as personal events (Snowden et al., 1994; Snowden et al., 1996a). Both Graham and Snowden have emphasized the important relationship between semantic memory and the forms of anterograde and remote memory needed to represent various forms of knowledge over the long term. Graham and her colleagues have hypothesized that the relatively intact hippocampus mediating episodic memory allows SD patients to acquire new information, but that dysfunctional temporal neocortex limits the ability of SD patients to consolidate autobiographical and remote factual information in semantic memory. This possibility is supported by the observation that patients with SD apparently are able to reacquire information such as the names of objects and to improve performance on measures such as category naming fluency with extensive practice (Graham et al., 1999). By comparison, Snowden and her colleagues have proposed that impaired semantic memory has unequal consequences for autobiographical and factual forms of remote memory in SD since these remote forms of memory are dissociable and have distinct neural representations in temporal neocortex. This view converges with other recent evidence suggesting an alternate account: The breakdown of semantic memory in SD represents a regression from context-free meaning to highly specific, personal, and context-dependent meaning (Bozeat et al., 2001). Regardless of the specific nature of the remote memory impairment in SD, these findings appear to be most consistent with a modality-neutral form of semantic memory.

**Impaired reading and writing**

There is considerable evidence suggesting, however, that the semantic memory impairment in SD is modality-specific in nature. One such source of evidence comes from SD patients’ difficulty with reading. Warrington’s (Warrington, 1975) initial cases revealed surface dyslexia, that is, a pattern of reading impairment where irregularly-spelled words are particularly difficult to pronounce correctly. Regularization errors are very common, where the words are pronounced in a manner that obeys letter-sound correspondence rules and parallels similarly-spelled words in English (Patterson and Hodges, 1992; Patterson et al., 1994; Noble et al., 2000). These patients appear to have relatively little difficulty with regularly-spelled words, suggesting that the deficit is not visually-based. Since the pronunciation of irregularly-spelled words must be memorized and cannot be determined on the basis of grapheme-phoneme correspondence rules, surface dyslexia in SD may be due to the modality-specific degradation of lexical phonological representations.

Additional evidence that this impairment may be due to a modality-specific deficit for representing visual forms of words comes from SD patients’ difficulty with irregularly-spelled words in other contexts. For example, SD patients frequently have surface dysgraphia, with spelling difficulty and regularization errors in writing. Examples of surface dysgraphia come from Parkin’s (Parkin, 1993) patient, who frequently misspelled irregular words such as “colonel” (spelled “curnal”) and “soldiers” (spelled “solgers”). Baxter and Warrington (Baxter and Warrington, 1987) showed that their patient’s spelling was affected by regularity but not by word frequency or word class. Another SD patient was said to have a “surface dysphasia”, manifested as impaired repetition of irregularly-spelled words (McCarthy and Warrington, 2001).

An alternate approach posits a specific causal link between SD patients’ reading difficulty and a modality-neutral semantic memory deficit. Patterson and her colleagues have argued that semantic memory is necessary to bind together the sublexical elements of sight vocabulary words so that they can be pronounced with minimal phonologic mediation such as grapheme-phoneme correspondence rules (Patterson and Hodges, 1992; Patterson et al., 1994). Evidence supporting this hypothesis comes from several sources. One longitudinal study of several SD patients showed parallel decline in reading and writing irregularly-spelled words, and demonstrated a parallel decline in semantic memory (Graham et al., 2000). Another longitudinal study showed more accurate spelling of homophones when disambiguated by a syntactic context compared to a semantic context (Schwarz et al., 1998).

This account associating selective difficulty processing irregular words in SD to a modality-neutral semantic memory deficit has been extended recently to the disruption of past-tense inflectional morphology (Patterson et al., 2001). From the perspective of these investigators, forming the past-tense of a regular or weak verb involves looking up the word’s phonologic representation in the mental lexicon. These investigators inferred reasonably intact phonological representations from SD patients’ success at producing regular past tense forms (e.g. kick → kicked). However, irregular or strong verbs cannot depend on the phonological shape of the present-tense form to generate the past-tense form because the present-tense form of the word does not reliably predict the phonological
shape of the word’s past-tense form. Past-tense formation of irregular verbs nevertheless can be assisted by two factors. First, SD patients were able to generate the past-tense forms for some irregular verbs that are extremely frequent (e.g. do → did; go → went). Second, some strong past-tense verb forms benefit from a family resemblance (e.g. know → knew; blow → blew; throw → threw), and SD patients were somewhat successful at producing these. What of low frequency irregular verbs that cannot take advantage of these features? Constraint satisfaction models of inflectional morphology suggest that semantic representations of words can help generate the correct past-tense form of low frequency irregular verbs (Joannis and Seidenberg, 1999), but SD patients do not have this support because of their semantic memory deficit. Patterson and her co-workers in fact found that SD patients have significant difficulty forming the past-tense of low frequency irregular verbs (Patterson et al., 2001).

It is important to point out in this context that impaired semantic memory does not necessarily lead to impaired spelling of irregular words in SD (Cipolotti and Warrington, 1995; Lauro-Grotto et al., 1997; Schwarz et al., 1998). This brings us back to modality-specific difficulty accessing phonologic representations, where surface dyslexia and regularization errors may be due to difficulty accessing phonology from semantics (Watt et al., 1997). This would also explain cases of progressive anoma, where semantic representations are relatively preserved but are disconnected from the lexical phonological representations needed for naming (Graham et al., 1995; Lambon Ralph et al., 2001). From this perspective, deficits in these patients may be related to the specific neuroanatomic distribution of disease, where reading, writing, and visual feature knowledge for objects are modality-specific representations in adjacent brain regions that may or may not be affected in a particular patient with SD. Consistent with this approach, one report described reading difficulty in SD that progresses from surface dyslexia to letter-by-letter reading, a form of reading difficulty attributed to impoverished letter recognition regardless of semantic memory status (Noble et al., 2000). These investigators argued that this modality-specific pattern of reading difficulty in SD may reflect the anatomic distribution of disease as the condition progresses.

Taken together, these observations suggest that patients with SD are limited in their comprehension of words, in the non-verbal knowledge that is associated with these words, and in the ability to use these words effectively on tasks such as confrontation naming and reading. There is much evidence consistent with the claim that a modality-neutral semantic deficit underlies these impairments. Thus, there appears to be relative difficulty for natural kinds compared to manufactured artifacts, and this appears to be independent of visual-perceptual feature knowledge. Entailments of a modality-neutral deficit in semantic memory may include difficulty reading and writing low frequency words with irregular spelling, and impoverished remote memory. Alternately, SD patients may have a modality-specific impairment that affects categories of knowledge unequally, with object knowledge being more sensitive to degradation than knowledge of abstract concepts or number knowledge. A modality-specific degradation of visual-perceptual features may play an important role in the impaired mental representation of natural kinds. Other work emphasizes a modality-specific deficit for phonological representations, such as impaired lexical retrieval on naming tasks, and difficulty with the connections between a semantic representation and its lexical phonological representation. However, there does not appear to be strong evidence in the cognitive literature at present to support the claim that the semantic memory deficit in SD can be explained entirely by dissociable forms of progressive fluent aphasia related to modality-specific impairments, such as a progressive anomic syndrome due to a compromised phonologic representation or a deficit for object knowledge due to the modality-specific degradation of visual-perceptual feature knowledge. Such evidence may come from imaging studies of carefully characterized patients that test hypotheses concerning modality-specific representations in adjacent brain regions.

**Neuroimaging features of SD**

Early CT imaging studies of semantically impaired patients provided by Warrington (Warrington, 1975) and Mesulam (Mesulam, 1982) revealed some non-specific atrophy that was greater in the left hemisphere than the right hemisphere. Unfortunately, CT imaging provides only limited structural detail since this modality has significant bony artifact that prevents adequate imaging of the temporal lobe. One of Warrington’s (Warrington, 1975) patients was re-imaged with MRI, revealing left-sided peri-Sylvian and temporal atrophy (Tyrrell et al., 1990).

More recent work has attempted to define in greater detail the distribution of atrophy in patients with SD. An anterior-posterior gradient of asymmetric atrophy of the left temporal lobe was observed in a series of 10 SD patients, based on experimenter-implmented regional analyses of high resolution MRI (Chan et al., 2001b). Areas of atrophy included entorhinal cortex, parahippocampal gyrus, fusiform gyrus, superior, middle and inferior temporal gyri, and medial temporal structures such as the amygdala and the hippocampus. Several investigators, focusing on medial temporal structures, have confirmed hippocampal atrophy in SD that is more prominent in the left hemisphere, and have emphasized the relatively anterior distribution of hippocampal atrophy in these patients (Frisoni et al., 1999; Laakso et al., 2000). A longitudinal study analyzed volumetric change of anterior and posterior halves of the left hemisphere and the right hemisphere (Chan et al., 2001a). The annualized rate of atrophy in the left anterior quadrant of SD patients was 3.6%, greater than the annualized atrophy rate in the right anterior quadrant (2.6%). Atrophy in these anterior quadrants proceeded at a faster rate than in the posterior quadrants of the left hemisphere (2.1%) or the right hemisphere (1.5%).
Other work has correlated cognitive difficulty with regional atrophy in SD. Using a voxel-based morphometric analysis of high resolution structural MRI in 6 SD patients, cortical atrophy was found in the temporal pole bilaterally, in middle, inferior, and anterior fusiform gyri of the left temporal lobe, and in ventromedial cortex in the left frontal lobe (Mummery et al., 2000). Poor performance on a measure of semantic memory correlated with atrophy of the left temporal pole but not with left ventromedial frontal cortex. A follow-up study with 18 SD patients showed a similar pattern of atrophy affecting primarily the left temporal lobe, based on experimenter-drawn cortical regions (Galton et al., 2001). Performance on a measure of semantic memory correlated with atrophy of the left fusiform gyrus, while naming difficulty correlated with atrophy of polar, middle, and inferior temporal regions of the left hemisphere. In another study implementing an automated high-dimensional normalization and segmentation analysis in 8 SD patients, examination of gray matter atrophy on high resolution structural MRIs showed significant atrophy that was most prominent in the left lateral temporal cortex, left fusiform gyrus, left inferior temporal gyrus, and the left temporal pole (Grossman et al., 2004). Difficulty on a measure of semantic memory correlated with left inferolateral portions of left temporal cortex. However, difficulty with the lexical retrieval component of a confrontation naming task correlated with left anterior lateral temporal atrophy. These findings emphasize left temporal lobe atrophy in SD, and appear to correlate this distribution of atrophy with impairments of naming and semantic memory that are not homologous.

Functional neuroimaging studies obtained at rest have attempted to confirm the critical role of left temporal lobe functioning in this syndrome. A PET study of one of Warrington’s (Warrington, 1975) semantically-impaired patients and three additional SD patients revealed significantly reduced oxygen utilization in left temporal and peri-Sylvian regions (Tyrrell et al., 1990). SPECT imaging in a progressive fluent aphasic revealed left hemisphere hypoperfusion that appeared to be most evident in the temporal region (Pocek and Luzzatti, 1988). In Snowden’s series, six progressive fluent aphasics studied with SPECT imaging revealed hypoperfusion anteriorly that involved the left hemisphere in two patients and was bilateral in four patients (Snowden et al., 1992). The PET scans of two progressive fluent aphasics showed glucose hypometabolism that was most prominent in the posterior temporal and inferior parietal regions of the left hemisphere (Kempler et al., 1990). Thus, there is considerable evidence that SD patients have reduced activity in the left hemisphere that appears to be centered in the left temporal lobe.

A SPECT activation study revealed reduced left temporal activation during semantic decisions in SD (Cardebat et al., 1996). A PET activation study of four SD patients confirmed the crucial role of the left temporal region in this clinical syndrome by assessing the pattern of cortical activation associated with a semantic decision about pictures (Mummery et al., 1999). SD patients demonstrated limited recruitment of the left posterior inferior temporal gyrus, an area thought to be crucial to semantic functioning since it is activated by control subjects during performance of the same semantic decision task. The investigators attributed the pattern of limited activation to a disconnection within the left temporal lobe separating the atrophic anterior temporal regions from the crucial semantic cortices of posterior temporal regions.

These findings suggest that the left temporal lobe plays a crucial role in the semantic impairment of SD patients, although additional work is needed to determine more precisely the role that these temporal regions play in SD. While some work appears to indicate that a modality-neutral deficit due to left inferolateral or polar disease underlies the semantic memory impairment of SD, other studies cannot rule out the potential contribution of a modality-specific impairment for visual-perceptual features in inferior temporal cortex or lexical phonological representations in left lateral temporal cortex. It would be important to contrast imaging studies in well-characterized SD patients with specific impairment patterns in order to test modality-neutral and modality-specific accounts of impaired semantic memory in SD.

Conclusion

Is there a single progressive aphasic syndrome? Or are there many? Longitudinal observations of individual PPA patients suggest a transition within individual subjects over time – for example, patients who present with a fluent form of progressive aphasia and gradually demonstrate more of a non-fluent aphasic profile as the disease progresses (Mesulam, 2001). Cases of progressive mixed aphasia also show features of both PNFA and SD at one time. However, published cross-sectional and longitudinal observations directly comparing these patients overwhelmingly seem to indicate that there are distinct syndromes of PNFA and SD (Hodges and Patterson, 1996; Snowden et al., 1996b; Neary et al., 1998). This is supported further by imaging studies showing distinct patterns of cognitive-cortical correlations in direct comparisons of PNFA and SD (DeVita et al., 2002; Grossman et al., 2004). The algorithm we use to identify subgroups of PPA patients, based on a modification of published criteria (Neary et al., 1998) to improve reliability, is provided in the appended tables (Davis et al., 2001; Price et al., 2001).

Recently, appellations such as “temporal-variant” and “frontal-variant” have been suggested to label aphasic and non-aphasic subgroups of FTD patients, respectively. However, the clinical-anatomic associations implied by these labels may be premature: PNFA is an aphasic syndrome associated with a frontal distribution of disease, for example, and PNFA does not necessarily involve behavioral difficulty. Observations such as the association of a progressive aphasic syndrome with a frontal distribution of disease in FTD thus call to question anatomically-based terms such as “frontal-variant” and “temporal-variant”.

This perspective nevertheless raises important questions about the clinical and anatomic subgrouping of progressive
aphasics. While patients with PNFA and SD may be identified on the basis of relatively distinct behavioral and imaging profiles, there may be finer-grained divisions within each progressive aphasic subgroup that have not been addressed. These finer-grained distinctions are potentially important for clinical purposes. Moreover, they have important entailments for our understanding of the neural representation of language. Some PNFA patients thus appear to have grammatical limitations, but other PNFA patients demonstrate a material-specific, phonologically-based deficit without agrammatism. SD patients may have a modality-neutral impairment of semantic memory, or various combinations of modality-specific deficits that depend on the precise distribution of disease. While there may be some clinical evidence for these distinctions, there is little converging evidence from longitudinal or neuroimaging studies at present to support these finer distinctions within PNFA or SD. The answers to these questions have important consequences for characterizations of language functioning and improving our understanding of the way in which the brain supports these language functions.

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Appendix

Subgroup criteria

Progressive non-fluent aphasia

Core Diagnostic Criteria
A. Insidious onset and gradual progression for 24 months
B. Decline in:
   1. Fluent speech (i.e., speech is nonfluent, telegraphic, effortful, impaired articulatory agility).
   2. Grammar – (i.e., aggrammatism is present – omission or incorrect use of grammatical terms, including articles, prepositions, auxiliary verbs, etc.)
C. Preserved:
   1. Anterograde memory (i.e., intact recognition testing for list learning and visual paradigms)
   2. Early preservation of interpersonal conduct
   3. Comprehension and general factual knowledge (semantic knowledge)

Supportive Diagnostic Criteria
A. Anomia; inability to find correct word, prolonged latencies between words
B. Phonemic (literal) paraphasic and sound-based errors ('pat' for 'bat'); phonemic transpositions ('animal' for 'animal') and omissions (e.g., 'amal' for 'animal')
C. Agrammatic comprehension
D. Dysarthria

Semantic dementia

Core Diagnostic Criteria
A. Insidious onset and gradual progression
B. Decline in:
   1. Conversational Content (i.e., empty speech despite intact phrase length)
   2. Comprehension of single words
   3. Naming (anomia) and/or semantic paraphasias
C. Preserved:
   1. Fluent speech (e.g., multisyllabic repetition and automatic sequences preserved)
   2. Anterograde memory (i.e., intact recognition testing for list learning and visual paradigms)
   3. Early preservation of interpersonal conduct

Supportive Diagnostic Criteria
A. Press of speech, idiosyncratic word usage
B. Surface dyslexia, or letter-by-letter reading; surface dysgraphia, or regularization errors in spelled words (preserved reading and writing orthographically regular words)
C. Preserved calculation, abstract words

Progressive mixed aphasia

Core Diagnostic Criteria
A. Insidious onset and gradual progression
B. Decline in:
   At least ONE of the following Non-fluent Aphasia signs:
   1. Fluent speech (i.e., speech is nonfluent, telegraphic, effortful, speech; unable to produce a grammatical sentence; impaired articulatory agility)
   2. Grammar – (i.e., aggrammatism is present – omission or incorrect use of grammatical terms, including articles, prepositions, auxiliary verbs, etc.)
AND:
   At least ONE of the following Fluent Aphasia signs:
   1. Conversational Content (i.e., empty speech)
   2. Comprehension ability for single words
   3. Naming (anomia) and/or semantic paraphasias
C. Preserved:
   1. Anterograde memory (i.e., intact recognition testing for list learning paradigms)
   2. Early preservation of interpersonal conduct