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Progressive language impairments: definitions, diagnoses, and prognoses

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Background: Speech pathologists have much to contribute to diagnosis of, intervention in, and education about the clinical syndromes that present with selective and progressive impairments in spoken or receptive language processing, reading, writing, and semantic knowledge. However, there is no single agreed classification system for these disorders, with the result that different research and clinical groups may use the same terms with subtly or substantially different meanings, or use different terms for similar phenomena. Understanding of the neuropathology and prognosis of these disorders is increasing rapidly.

Aims: This paper reviews (i) the major approaches to classifying the clinical presentations of these disorders, (ii) progress in relating the clinical syndromes to neuropathology, and (iii) currently available information about prognoses.

Main Contribution: Two main classification approaches based on clinical syndromes have emerged for these disorders. The first uses the label primary progressive aphasia to describe gradual and selective deterioration in word finding, object naming, or word comprehension without identifying subtypes, following criteria published by Mesulam and colleagues during and subsequent to 2001. The second approach, initially associated with the Lund consensus meetings in the 1990s, identifies the clinical syndromes of nonfluent progressive aphasia (with and without apraxia of speech) and semantic dementia as subtypes of frontotemporal dementia. There are two main neuropathologies responsible for progressive language impairments: a spectrum of diseases classed under the term frontotemporal lobar degeneration, and Alzheimer’s disease. Semantic dementia is most often associated with frontotemporal lobar degeneration with motor neuron disease-type inclusions. Apraxia of speech in neurodegenerative disease is most often associated with the tau-positive subtypes of frontotemporal lobar degeneration. Alzheimer-type neuropathology has been found in both semantic dementia and nonfluent progressive aphasia. Information about survival and autonomy in these disorders, and about incidence of behaviour and personality change and motor impairment, is just beginning to emerge.

Conclusions: The range of classification systems in use emphasise the importance of specifying the criteria used to reach a particular diagnosis, and the clinical symptoms on which the diagnosis is based. As pharmacological or other treatments become available to target the neuropathological mechanisms in these diseases, a primary diagnostic goal will be to identify the likely neuropathology in order to match clients to appropriate therapies at the earliest opportunity.

Keywords: Primary progressive aphasia; Frontotemporal dementia; Semantic dementia; Diagnosis; Prognosis.
As recently as 20 years ago, speech pathology training made little or no mention of the management of speech, language, and communication changes associated with dementia. The speech pathologist’s role was limited to differential diagnosis between language impairments associated with dementia and language impairments subsequent to stroke. Since then there has been growing recognition that progressive brain pathology can result in selective language impairments where the expertise of the speech pathologist is invaluable.

This shift has come about for four main reasons. First, knowledge of the diseases that cause dementia has increased exponentially as the ageing population in both the developed and developing worlds provides an increasing number of people at risk for dementia (di Carlo, Baldereschi, Inzitari, & Amaducci, 1999). Second, progress in cognitive theory and neuropsychological assessment has allowed a more precise understanding of the cognitive and behavioural changes that occur in these diseases. Third, advances in imaging technologies reveal the integrity of brain structure and function in vivo. Finally, rapid developments in molecular pathology made possible by large-scale brain tissue donation (McLean, Beyreuther, & Masters, 2001) are beginning to identify the causes of the degenerative changes in brain tissue. Alongside these groundbreaking shifts, earlier views of speech pathology practice that largely excluded people with dementia from a typical adult caseload are undergoing major change (Ripich & Horner, 2004).

A speech pathologist can now argue for a number of important roles on a dementia health and social care team. These include assessment, education of people with dementia and their families and communities, delivery of impairment- and activity- and participation-based speech, language, communication and swallowing interventions, and advocacy and policy development roles (Royal College of Speech and Language Therapists, 2005). There is a burgeoning literature on language, communication, and other neuropsychological interventions in dementia that considers the client within a holistic framework embracing physical health, cognitive strengths and limitations, and social and physical environment. Leading examples of these include Attix and Welsh-Bohmer (2006), Bayles and Tomoeda (1997), Bourgeois (1991), Bryan and Maxim (2006), Clare (2001), Killick and Allan (2001), Lubinski (1995), Lubinski and Orange (2000), and Ripich (1994).

In this context of growing interest in dementia, the subset of disorders in which there are selective and progressive impairments of language have received particular attention from the speech pathology community. The most well known of these is primary progressive aphasia (PPA, Mesulam, 1982, 2001; Mesulam & Weintraub, 1992). However, there is a broad constellation of clinical syndromes in which the most prominent, initial, and ongoing symptom is deterioration in spoken or receptive language processing, reading, writing, or some combination of these. There may or may not be other accompanying cognitive impairments. When a collective term is required in the current paper, such symptoms will be described as “progressive language impairments”.

Speech pathologists have much to contribute to diagnosis and intervention in these disorders because of the focal speech and language symptoms. Published work on appropriate interventions is only just beginning to appear, however, and lags behind the resources available on speech pathology interventions in dementia in
general. There is nonetheless a small emerging literature on this client group that includes expert opinion on therapy approaches (McNeil & Duffy, 2001; Robinson, 2001; Rogers, King, & Alarcon, 2000; Snowden & Griffiths, 2000; Thompson & Johnson, 2006), and two-to-three dozen or so published therapy reports ranging from descriptions of therapy activities included as part of a case report (Hart, Beach, & Taylor, 1997; Holland, McBurney, Moossy, & Reimnuth, 1985) to controlled studies (K. S. Graham, Patterson, Pratt, & Hodges, 1999; McNeil, Small, Masterson, & Tepanta, 1995; Schneider, Thompson, & Luhring, 1996), including the reports in this special issue of *Aphasiology*. We pick up some of the key themes emerging from this literature in the final paper of this special issue (Croot, Nickels, Laurence, & Manning, 2008 this issue).

At this point in time we have much to learn about optimal interventions for progressive language impairments. Many crucial questions, such as “Which intervention for which client?”, “Which intervention at which stage in disease progression?”, “How long should therapy be continued?”, “What will the benefits be?”, and “How well can treatment effects be maintained?” are still a long way from evidence-based answers. Further, there are indications that people with these disorders are under-referred for speech pathology services (Taylor, Kingma, Croot, & Nickels, 2008 this issue), a situation that can be improved with increased awareness of available therapy options. This paper will address some commonly-asked questions about progressive language impairments which are relevant background for those considering providing intervention: questions about the range of clinical presentations, the disease processes involved, and the likely prognosis for various clinical presentations.

MANY DIAGNOSTIC CATEGORIES: CLINICAL SYNDROMES AND NEUROPATHOLOGY

One does not have to read far in the literature on progressive language impairments before encountering a range of diagnostic labels, such as fluent progressive aphasia, semantic dementia, progressive non-fluent aphasia, primary progressive anoma, progressive apraxia of speech, dementia of the frontal type, primary progressive dysgraphia, and (many) others in similar vein. References to frontotemporal lobar degeneration (FTLD), Pick’s disease, and dementia lacking distinct histology (DLDH) are likely to be close behind. There are two main reasons for this “bewildering array of diagnostic terms” (Hodges & Miller, 2001, p. 31): (i) the distinction between labels for clinical syndromes and neuropathological classifications, and (ii) the independent development of several classification systems towards the end of the twentieth century.

Clinical syndromes

Some classification labels (for example, fluent progressive aphasia, semantic dementia, progressive non-fluent aphasia, progressive apraxia of speech, dementia of the frontal type, primary progressive dysgraphia) primarily describe the *clinical syndrome*, i.e., the particular set of symptoms with which the client presents at the clinic. Others (for example, frontotemporal lobar degeneration, Pick’s disease, and dementia lacking distinct histology) primarily imply the *neuropathology* (neurodegenerative disease process) presumed or proven to be present in the brain (Hodges & Miller, 2001).
The range of signs and symptoms that make up the clinical syndrome presented by a person with neurodegenerative disease reflect the location of damaged tissue in the brain (Mesulam, Grossman, Hillis, Kertesz, & Weintraub, 2003; Neary, 1999), just as they do in acquired language disorders caused by stroke, traumatic brain injury, or tumour. In the case of progressive language impairments, the neuropathologies involved may target any one or more of a number of frontal, temporal, parietal, and/or subcortical regions involved in a range of speech and language functions. Speech, language, communication, and other abilities that were previously reliant on these brain regions will be compromised, and the person, their family, and colleagues will begin to notice a decline in those abilities. Because any or many parts of the brain networks supporting speech and language may be affected by the disease process involved, there are diverse patterns of speech and language symptoms that may develop. Further, the functioning of a particular brain region may be affected either directly when tissue in that region is diseased, or indirectly when it is connected in a brain network to another structure that is diseased, resulting in distal or "diaschisis" effects (Hillis et al., 2002; Price, Warburton, Moore, Frackowiak, & Friston, 2001). For example, the anomia in semantic dementia is attributed to hypoperfusion (reduced blood flow) in posterior temporal regions thought to be caused by the neuropathology located in the anterior temporal lobe (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001; Mummery et al., 1999).

**Frontotemporal dementia**

One of the most important syndrome labels found in the literature on progressive language impairments is **frontotemporal dementia** (FTD), which refers to a range of non-Alzheimer-type dementia syndromes caused by focal atrophy of the frontal and anterior temporal brain regions (Hodges, Davies, Xuereb, Kril, & Halliday, 2003; Hodges et al., 2004). The earliest and dominant symptom in frontotemporal dementia is often a gradual and progressive speech and/or language impairment (the **language variant of frontotemporal dementia**; McKhann et al., 2001), yielding clinical syndromes characterised by progressive language impairments. An earlier term for the language variant was **temporal (lobe) variant of frontotemporal dementia** (e.g., Edwards-Lee et al., 1997), so-named because of the brain region most affected in these cases.

A second major category of frontotemporal dementia primarily involves progressive changes in behaviour, including personality change and socially inappropriate behaviour (McKhann et al., 2001). This **behavioural variant of frontotemporal dementia** (also called **frontal variant frontotemporal dementia**; Hodges & Miller, 2001) will not be addressed in detail in this paper. However, behaviour changes do often emerge with progression in cases of progressive aphasia, (as neuropathology spreads to brain regions responsible for these functions), so these will be discussed in relation to disease progression and prognosis.

**Neuropathology**

The neuropathological findings in frontotemporal dementia include a spectrum of disease processes described under the umbrella term of **frontotemporal lobar degeneration** (FTLD; McKhann et al., 2001). There are a range of alternative
names and classifications for these neuropathologies, described in more detail below. Sometimes, however, a person can present with clinical symptoms unlike classical Alzheimer-type dementia and consistent with those described for frontotemporal dementia, but be found to have Alzheimer-type neuropathology at autopsy. Thus the other major disease associated with progressive language impairments is Alzheimer’s disease (Hodges et al., 2003; Knibb, Xureb, Patterson, & Hodges, 2006). Neuropathological diagnosis is almost always made at autopsy following donation of brain tissue, although in rare cases biopsy may be used to rule out infection and cancer. Standard diagnostic criteria for Alzheimer’s disease do not allow entirely reliable differentiation between Alzheimer’s disease and frontotemporal lobar degeneration during life (Varma et al., 1999), and many studies in recent years have sought to refine the diagnostic criteria for these two diseases (Mendez & Perryman, 2002; Rascovszky et al., 2002; Rosen et al., 2002).

Classification systems developed by different research teams

Investigations of progressive language disorders took off in a number of centres in Europe and North America from the 1980s onwards. It was apparent from early on that there was considerable similarity between clinical presentations that were later shown to be associated with different neuropathologies and, conversely, that there were similar neuropathology findings post-mortem for syndromes that had been clinically dissimilar in life. To some extent, various research centres found different coherent ways of carving the clinical presentations and neuropathologies into diagnostic categories; sometimes creating new labels and new categories, and sometimes defining existing categories in slightly different ways.

The following section describes some of the major clinical classification systems currently in use. The range of classification systems, and the fact that different research groups may use somewhat different criteria in applying the same diagnostic label, emphasise the need for speech pathologists to be specific about which criteria they are using in reaching a particular diagnosis.

CLASSIFICATION SYSTEMS BASED ON CLINICAL SYNDROME

There is no single agreed classification system for progressive language impairments (Josephs et al., 2006a), with Knibb et al. (2006), for example, identifying five prominent approaches in current use. However, two main classification approaches based on clinical syndromes have emerged: one that summarises a range of progressive language impairments under the label *primary progressive aphasia*, and one that makes a core distinction between the syndromes of semantic dementia and non-fluent progressive aphasia (Hodges & Patterson, 1996; Neary, 1999) within the broader diagnostic category of frontotemporal dementia. Below are outlined the development of the current criteria for diagnosing primary progressive aphasia, then summarise the alternative approach taken by the Lund group of researchers and recent developments within this approach.

Primary progressive aphasia: Early reports and subtypes

The diagnosis of *primary* progressive aphasia (italics added) as described by Mesulam and colleagues (Mesulam, 1982, 1987, 1990, 2001; Mesulam et al., 2003;
Mesulam & Weintraub, 1992) is reserved for people with gradual language decline over a period of at least 2 years, with language difficulties being the only factor compromising activities of daily living (Mesulam & Weintraub, 1992; Weintraub, Rubin, & Mesulam, 1990). The early reports (Mesulam, 1982, 1987) described individuals for whom the deficits were predominantly language-based over a long period (up to 10 years) without generalised dementia, thus the neuropathological process was presumed to differ from Alzheimer’s disease. Today a diagnosis of primary progressive aphasia is still assumed to indicate a non-Alzheimer pathology for some research and clinical groups—however, as described below, a person may meet current clinical criteria for primary progressive aphasia (Mesulam, 2001), yet prove to have Alzheimer-type pathology at post-mortem investigation.

The earliest explicit classification of progressive language impairments distinguished three subtypes of primary progressive aphasia along a fluency dimension, with a broad division into fluent, non-fluent and mixed subtypes (Grossman & Ash, 2004; Mesulam & Weintraub, 1992; Snowden, Neary, & Mann, 1996). The fluent subtype was defined by phrase length greater than four words and grammatically intact language, with language resembling anomic, conduction, Wernicke’s, and transcortical sensory aphasia as defined by the “classical” aphasia batteries (Mesulam & Weintraub, 1992). Some of the (otherwise) fluent cases were noted to have word-finding difficulties that introduced long pauses into their spoken language, a subtype of fluent primary progressive aphasia that Mesulam and Weintraub described as logopenic. The non-fluent subtype was characterised by agrammatic speech with reduced phrase length, resembling Broca’s and transcortical motor aphasias. An earlier report by the same authors had emphasised the prominence of errors in the production of speech sounds in four non-fluent cases (Weintraub et al., 1990), thus for some researchers and clinicians the presence of phonological or articulatory errors came to be viewed as the hallmark of the non-fluent subtype. Mixed primary progressive aphasia was proposed as the classification for people who met criteria for the non-fluent subtype but also had comprehension difficulties, a presentation resembling a global aphasia.

Snowden et al. (1996) described three very similar profiles, but noted that a number of the fluent cases (with fluent spoken language, anomia, and word comprehension deficits) also had difficulties recognising and knowing about objects and people, and developed personality and behaviour change with disease progression. They called this presentation semantic dementia (Snowden, Goulding, & Neary, 1989). However, Mesulam and colleagues (Mesulam, 2001; Mesulam et al., 2003) exclude people with semantic dementia defined this way (progressive loss of knowledge about objects and people occurring alongside a fluent progressive aphasia) from a diagnosis of primary progressive aphasia, and consider this a “primary progressive aphasia-plus syndrome” (see below). Confusingly, the term “semantic dementia” is sometimes used to label fluent progressive aphasia with impaired word comprehension without loss of object and face knowledge. For some groups this is on the basis that such deficits are expected to develop with disease progression, but for others the terms fluent progressive aphasia and semantic dementia are taken to be interchangeable. It is essential, therefore, to specify what deficits are present when using the label “semantic dementia” (Mesulam et al., 2003).

One of the clinical difficulties that has been faced by speech pathologists trying to apply the fluent/non-fluent categorisation is that the progressive language impairments encountered in the clinic and described in the published literature do
not neatly correspond to the fluent versus non-fluent aphasia profiles associated with CVA (Josephs et al., 2006a; Mesulam, 2001). The problem is compounded by the fact that the fluency distinction is not straightforward in the CVA population (Gordon, 1998), and by clinical data showing that a high proportion of people with primary progressive aphasia may be fluent early in the disease course but progress to a non-fluent profile of language production over time (Kertesz, Davidson, McCabe, Takagi, & Munoz, 2003). Further, for clinicians who viewed the presence of phonological errors as diagnostic of the non-fluent subtype, clients who presented with phonological errors and fluent speech, or effortful, non-fluent speech without phonological errors, were particularly difficult to categorise. Mesulam and colleagues now acknowledge that basing a diagnosis of primary progressive aphasia subtype on the person’s fluency is far from straightforward (Mesulam et al., 2003).

Current criteria for primary progressive aphasia: De-emphasis of subtypes

For the above reasons, Mesulam and colleagues (Mesulam, 2001, 2003; Mesulam et al., 2003; Sonty et al., 2002) have more recently taken a different approach that has been widely adopted in the USA, describing what is essentially a single category of primary progressive aphasia using the diagnostic criteria reproduced in Table 1. The central requirement is “insidious onset and gradual progressive impairment of word-finding, object naming, syntax or word comprehension” evident in conversation or formal assessment over a 2-year period (Mesulam, 2003, p. 1536). The aphasia may be fluent or non-fluent (Mesulam et al., 2003).

Structural brain imaging—i.e., using computerised tomography (CT) or structural magnetic resonance imaging (MRI)—in primary progressive aphasia shows tissue loss (atrophy) in frontal, temporal, and parietal regions associated with the left hemisphere language network (Mesulam, 2001). In the study of Josephs et al. (2006a), a group of participants with primary progressive aphasia without agrammatism, apraxia of speech, or semantic dementia had predominantly left-sided posterior temporal

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**TABLE 1**

<table>
<thead>
<tr>
<th>Diagnostic criteria for primary progressive aphasia</th>
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<tbody>
<tr>
<td>1. Insidious onset and gradual progression of word-finding, object-naming, or word-comprehension impairments as manifested during spontaneous conversation or as assessed through formal neuropsychological tests of language.</td>
</tr>
<tr>
<td>2. All limitation of daily living activities attributable to the language impairment, for at least 2 years after onset.</td>
</tr>
<tr>
<td>3. Intact premorbid language function (except for developmental dyslexia).</td>
</tr>
<tr>
<td>4. Absence of significant apathy, disinhibition, forgetfulness for recent events, visuospatial impairment, visual recognition deficits or sensory-motor dysfunction within the initial 2 years of the illness. (This criterion can be fulfilled by history, survey of daily living activities, or formal neuropsychological testing.)</td>
</tr>
<tr>
<td>5. Acalculia and ideomotor apraxia may be present even in the first 2 years (mild constructional deficits and perseveration—as assessed in the go–no-go task—are also acceptable as long as neither visuospatial deficits nor disinhibition influences daily living activities).</td>
</tr>
<tr>
<td>6. Other domains possibly affected after the first 2 years but with language remaining the most impaired function throughout the course of the illness and deteriorating faster than other affected domains.</td>
</tr>
<tr>
<td>7. Absence of specific causes such as stroke or tumour as ascertained by neuroimaging.</td>
</tr>
</tbody>
</table>

atrophy. Although structural imaging is typically one of the earliest investigations performed, functional brain imaging is likely to be more sensitive at the early stages in identifying regional changes associated with progressive language impairments, showing abnormalities earlier than structural imaging (Mesulam, 2001; Sinnatamby, Antoun, Freer, Miles, & Hodges, 1996). Such techniques include single positron emission tomography (SPECT) imaging, positron emission tomography (PET) imaging, perfusion-weighted MRI, and electroencephalography (EEG). Functional imaging of people with primary progressive aphasia shows that activation of classical language areas may be normal, although additional brain regions may participate in compensatory and/or increased inhibitory activity (Sonty et al., 2002).

Under the current approach of Mesulam and colleagues, people who initially receive a diagnosis of primary progressive aphasia but subsequently develop non-language symptoms (personality or behaviour or extrapyramidal motor symptoms, or neurological signs consistent with motor neuron disease) are said to have a primary progressive aphasia-plus syndrome (Mesulam, 2001; Mesulam et al., 2003).

Semantic dementia and non-fluent subtypes of FTD

An alternative approach more common in Europe was strongly influenced by meetings on frontotemporal dementia held in Lund, Sweden, (Neary, 1999; The Lund and Manchester Groups, 1994) describing two main clinical presentations in which there is progressive language decline: semantic dementia and non-fluent progressive aphasia (identical to progressive non-fluent aphasia).

Semantic dementia, according to the early definitions (Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden et al., 1989), is characterised by striking anomia and impaired word comprehension attributed to loss of semantic memory (e.g., concepts, facts, semantic features) (Hodges & Miller, 2001; Knibb et al., 2006). As noted by Snowden et al. (1989), these semantic memory deficits also impair recognition of visually presented objects, a symptom known as visual agnosia (Neary, 1999). This is the predominant usage of the term “semantic dementia”, and in this sense the term is not interchangeable with a diagnosis of fluent primary progressive aphasia as defined by Mesulam and colleagues (Mesulam, 2001; Mesulam et al., 2003), as discussed above.

The early reports of imaging in semantic dementia were based on visual inspection of structural CT and MR images (Hodges et al., 1992; Snowden et al., 1996). These noted the consistently striking and focal atrophy of anterior temporal regions, especially the infero-lateral regions of the temporal pole visible on coronal MRI. All individuals showed left temporal atrophy, with involvement of anterior right temporal regions apparently associated with more severe object recognition deficits (Snowden et al., 1996). More recent studies that have sought to quantify the degree of atrophy have revealed that changes may be bilateral or involve the left hemisphere more than the right, and involve medial temporal structures, including the hippocampus and amygdala as well as infero-lateral regions (Chan et al., 2001; Galton et al., 2001; Gorno-Tempini et al., 2004).

Nonfluent progressive aphasia is defined by non-fluent spontaneous speech, and at least one of the following: anomia, errors in production of speech sounds, or

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1 For example, muscle weakness and atrophy, fasciculations, hyperactive reflexes, and spasticity (Borasio, Appel, & Buettner, 1996).
grammatical errors (Knibb et al., 2006; Neary, 1999). More recently, Gorno-Tempini et al. (2004) suggested that two non-fluent categories of primary progressive aphasia should be distinguished. One category they continued to call non-fluent progressive aphasia, characterised by apraxia of speech and agrammatism/syntactic comprehension deficits with spared single word comprehension. The other they called logopenic progressive aphasia, describing a clinical presentation with slow speech, impaired syntax comprehension, and anomia. Knibb et al. (2006) carried out a cluster analysis using 38 cases presenting with various progressive aphasia syndromes and also found that the non-fluent cases could be distinguished into two groups along the lines suggested by Gorno-Tempini et al. (2004).

In Gorno-Tempini et al.’s (2004) study, the subgroup of people with non-fluent progressive aphasia showed atrophy in Broca’s area (Brodmann areas 44 and 45), a small region of Brodmann area 47, and the left precentral gyrus of the insula. The people with logopenic progressive aphasia showed a completely different distribution of atrophy, with angular gyrus and the posterior third of the middle temporal gyrus most affected (Brodmann areas 39, 40, and 21), with additional atrophy in left anterior hippocampus, right angular gyrus and precuneus (Brodmann area 31).

In another recent approach, Kertesz, McMonagle, Blair, Davidson, and Munoz (2005) described six subtypes, including semantic dementia and three subtypes of primary progressive aphasia meeting Mesulam’s 2-year criterion: anomic, logopenic, and non-fluent primary progressive aphasia. Semantic dementia was defined by comprehension deficit, naming difficulty, and asking the meaning of nouns and objects (e.g., “What is parade?…shoe-polish?…steak?”; Kertesz et al., 2005, p. 2003). Anomic primary progressive aphasia described minimal impairment to fluency and speech rate but pronounced word-finding difficulty. Logopenic primary progressive aphasia described more severe word-finding difficulty combined with severely reduced output, but relatively preserved syntax, phonology, and articulation. Nonfluent primary progressive aphasia was characterised by agrammatism, errors in the production of speech sounds, and anomia. Kertesz et al. also noted two further subtypes: one they called aphemic, with difficulty in the production of speech approximately corresponding to apraxia of speech, and a mute subtype in which people were mute at presentation, but ambulant, cooperative and able to demonstrate relatively preserved comprehension.

In the newest development, Josephs et al. (2006a) advocated the need to distinguish when apraxia of speech is present, with or without aphasia. They noted that the non-fluent cases are frequently reported with “laboured speech”, “laboured articulation”, or “distortion of speech” (Josephs et al., 2006a, p. 1386), and suggested that the so-called “phonemic paraphasias” in these cases probably arise at an articulatory rather than a phonological level of processing. The perceptual features leading to a diagnosis of apraxia of speech by Josephs and colleagues (2006a, p. 1388) were consonant and vowel distortions; distorted sound substitutions; distorted sound additions; sound prolongations; trial and error attempts to correct articulation; slow overall rate; prolonged and often variable vowel duration and interword intervals; segregation of syllables; errors of stress assignment; and decreased phonetic accuracy with increased rate.

In this study, imaging of people with a selective progressive apraxia of speech showed atrophy to grey matter in superior premotor and supplementary motor areas, middle and inferior frontal gyri especially on the right, and basal ganglia (bilateral caudate and right globus pallidus). These individuals would not qualify for
a diagnosis of primary progressive aphasia according to the criteria of Mesulam and colleagues (Mesulam, 2001; Mesulam et al., 2003) because no language disorder is present. People with progressive non-fluent aphasia (primarily denoted by agrammatic or telegraphic speech) and apraxia of speech showed similar premotor atrophy but more posterior inferior frontal atrophy (Josephs et al., 2006a) than the people with apraxia of speech only.

HOW USEFUL ARE SYNDROME-BASED CLASSIFICATIONS?

Purpose and limitations of syndrome labels

A syndrome label that captures the primary symptoms can be clinically beneficial for communicating the nature of the symptoms among clinicians, and for relating a particular case to similar previous cases, including communicating to the person with one of these syndromes and their family that their condition is a recognised disorder. For example, in the most literal sense, the label “primary progressive aphasia” communicates that the person’s main (primary) symptom is an acquired language disorder (aphasia) that has a progressive course. Similarly, progressive pure anomia (K. S. Graham, Patterson, & Hodges, 1995) indicates that the progressive language disorder is primarily characterised by word-finding difficulties; primary progressive conduction aphasia (Hillis, Selnes, & Gordon, 1999) indicates there is similarity between the person’s language symptoms and one of the existing conceptualisations of conduction aphasia, and primary progressive apraxia of speech (Josephs et al., 2006a) suggests that speech, more than language, is the domain affected … and so on. Thus the proliferation of syndrome labels associated with these disorders provides a somewhat informative (if abbreviated) overview of the diversity of clinical presentations.

A problem arises, however, when different uses of a particular term by different researchers leads to misunderstanding about the clinical presentation being described. A syndrome label does not necessarily facilitate communication when there is no single agreed operational definition of the syndrome (Coltheart, 1984; Neary, 1999). For example, there are cases reported as semantic dementia with more or less comprehension impairment relative to anomia, or more or less behaviour and personality change. There are also people diagnosed with non-fluent progressive aphasia according to a range of definitions of “non-fluent”, with or without apraxia of speech, and even with or without aphasia (when apraxia of speech is the only symptom) (Josephs et al., 2006a). It is unfortunately but unavoidably the case at present that different groups of clinicians and researchers hold subtly or substantially different understandings as to what symptoms, features, or neuropathology are implied by a number of these syndrome labels. It is essential, therefore, to explicitly identify the classification system used to reach a diagnosis (e.g., Mesulam, 2001, or the Lund criteria described by Neary, 1999 etc.), and to describe in detail the presenting symptoms, rather than simply assigning a syndrome label.

Change in syndrome with progression

Another difficulty in the application of syndrome labels to these disorders occurs because of the degenerative disease course. Impairments increase in severity over time and new impairments may become prominent that were not evident before. The
The clinical picture is far from static, and patterns of progression (as well as patterns of initial presentation) can be diverse.

It is not yet known to what extent the different neuropathologies responsible for progressive language impairments spread within language-specific networks of the brain versus spreading to brain regions involved in quite different cognitive functions. There are, however, three potential patterns of progression: (i) selective decline in language and/or speech abilities, (ii) initial language and/or speech decline, with additional impairments arising later in progression, and (iii) decline in language and/or speech alongside other deficits from onset.

To the extent that a person’s impairments remain selective to language over a long period (as in the rare cases where there are isolated language symptoms over a 10- to 20-year period; Mesulam, 1982; Schwartz, De Bleser, Poeck, & Weis, 1998), it can be assumed that language-specific networks alone are compromised. These would clearly meet criteria for primary progressive aphasia as defined by Mesulam and colleagues (Mesulam, 2001; Mesulam et al., 2003). For many years, Mesulam and colleagues have taken the position that a selective language disorder for the first 2 years is predictive of a more language-specific clinical course, and a non-Alzheimer-type neuropathology, and this is why the 2-year criterion is central to their diagnosis of primary progressive aphasia.

Other authors, however, prefer to drop the designation “primary” and use the shorter term, progressive aphasia (Knibb et al., 2006). These authors argue that the 2-year limit is arbitrary, that the presence or absence of non-language symptoms is only ever a matter of degree, and that people who satisfy the 2-year criterion happen to fall within one region of a broad continuum of possible symptoms associated with various neuropathologies, but do not otherwise represent a useful clinical category. Which of these views will prove to be correct remains an open question, as the research to support a distinctive prognosis for people meeting the 2-year claim has not yet been reported (Knibb et al., 2006; McNeil & Duffy, 2001). Nonetheless, McNeil and Duffy point out that the diagnostic label “primary progressive aphasia” is clinically helpful in highlighting the need for aphasia management as the central component of client care for as long as the deficits remain specific to language. They note, however, that the diagnosis of primary progressive aphasia may need to be altered if or when the person’s profile of impairments changes with disease progression (McNeil & Duffy, 2000).

In some cases, other deficits such as behavioural or personality change, impairments in additional cognitive domains (e.g., memory, visuo-spatial abilities, praxis, or attention), and non-speech motor impairments (gait rigidity, falls, vertical gaze palsy) can emerge during the disease course even when language impairments were the presenting symptom (profiles that Mesulam, 2001, would call primary progressive aphasia-plus syndromes). Diagnostic labels based on clinical symptoms alone clearly raise a problem in these disorders because a particular label may be appropriate at one point in time but not later. Kertesz et al. (2005) address this problem by describing the sets of clinical symptoms that emerge with disease progression in terms of the first syndrome, the second syndrome etc. For example, a person may have primary progressive aphasia (as per Mesulam’s 2001 definition) as their first syndrome, but later develop a second syndrome of behavioural problems typical of a frontal dementia in addition to the language syndrome, and perhaps later still a third syndrome, characterised by motor symptoms including rigidity, limb apraxia, and alien hand (Kertesz et al., 2005). Conversely, one or more aspects of
language decline can emerge later in a case for which other cognitive, behavioural, or motor deficits were the initial concern. In such cases, the language symptoms would constitute the second or third syndrome. Kertesz et al. (2005) use the term primary progressive aphasia when the language symptoms form the first syndrome for a period of 2 years or more, and call the disorder progressive aphasia when language decline is the second or third syndrome to appear.

The need for clinicopathologically based diagnostic categories

As pharmaceutical or other treatments become available to target the neuropathological mechanisms in these diseases, a primary diagnostic goal will be to identify the likely neuropathology in vivo, in order to match clients to appropriate therapies at the earliest opportunity. Even the development of such therapies requires “early and accurate prediction of pathology” (Davies et al., 2005, p. 1994; Whitwell et al., 2005). The most recent progress towards this goal comes from longitudinal studies analysing the clinical course and neuropathological findings in comparatively large case series of people who presented with or developed progressive language impairments (Davies et al., 2005; Hodges et al., 2003, 2004; Josephs et al., 2006a, 2006b; Kertesz et al., 2005; Knibb et al., 2006). These studies are beginning to clarify the relationship between the clinical course and the underlying disease process. The following section provides a brief introduction to the neuropathologies associated with progressive language impairments, then summarises current progress in relating clinical syndromes to the probable neuropathology. Finally, genetic mutations have been discovered in association with familial cases of frontotemporal lobar degeneration, and these will also be briefly reviewed.

NEUROPATHOLOGICAL DIAGNOSIS

Post-mortem examination of brain tissue classifies both the macroscopic and microscopic appearance of brain tissue. Macroscopic investigation notes regions of atrophy visible to the eye. Microscopic investigation (histology) involves treating slices of brain tissue with a range of chemical stains and agents that are sensitive to the molecular chemistry of a range of proteins that build up in the tissue in association with neurodegenerative disease. Treating the tissue with such techniques allows these atypical protein deposits (known as “inclusions”) to be seen under a microscope. The type, frequency, and location of these inclusions form the main basis for classifying different neurodegenerative diseases. The two neuropathologies associated with progressive language impairments are Alzheimer’s disease (Knibb et al., 2006), and the disease processes classed under the term frontotemporal lobar degeneration (or FTLD, McKhann et al., 2001).

Alzheimer’s disease

The hallmark neuropathological inclusions in Alzheimer’s disease are neurofibrillary tangles and neuritic plaques (The National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease, 1997), characterised by the proteins tau and beta amyloid, respectively. Although the atrophy in Alzheimer’s disease is usually widespread and symmetrical (Lantos & Cairns, 2001), it can be strikingly focal (localised to a small
region of the brain) in people with progressive language impairments (Galton, Patterson, Xuereb, & Hodges, 2000; Knibb et al., 2006). Differential diagnosis of Alzheimer’s disease versus frontotemporal lobar degeneration becomes more difficult in older individuals because of the increasing likelihood of neurofibrillary tangles and neuritic plaques with age (Johnson et al., 2005).

**Frontotemporal lobar degeneration**

Frontotemporal lobar degeneration is the current consensus term for a clinically and neuropathologically heterogeneous spectrum of diseases associated with the clinical syndrome of frontotemporal dementia. Diseases in the frontotemporal lobar degeneration spectrum were first reported by the German neurologist Pick (1892, 1904, cited in Kertesz, 2004), and are also described under the broad labels of *Pick’s Disease*, *frontal lobe degeneration of non-Alzheimer-type* (Brun, 1987) and *Pick complex* (Josephs et al., 2006b; Kertesz, Hudson, Mackenzie, & Munoz, 1994). There is ongoing discussion as to whether the neuropathological subtypes should be considered as separate disorders (e.g., Dickson, 1999) or as different points on a single disease spectrum (Josephs et al., 2006b). In this paper we treat them as related because the clinical symptoms co-occur in many cases, the diverse syndromes are associated with the same set of histological findings, and, in an inherited subtype known as *frontotemporal dementia and parkinsonism linked to chromosome 17* (FTDP-17), any of the clinical syndromes associated with frontotemporal dementia may occur (Josephs et al., 2006b; Kertesz, 2004; Neary, 1999).

In frontotemporal lobar degeneration there is focal atrophy of frontal and/or temporal regions (McKhann et al., 2001; Neary, 1999). There are a number of approaches to classifying the neuropathological entities involved, based on the type of inclusions present and their distribution in the brain. The inclusions can be categorised according to whether they test positive for tau (collectively called *tauopathies*), or for another protein called *ubiquitin* (Lantos & Cairns, 2001; McKhann et al., 2001). The presence or absence of tau or ubiquitin may prove to be important given current debate about whether prognosis is better for the tauopathies (Hodges et al., 2003; Josephs et al., 2006b; Kertesz et al., 2005), attempts to develop biochemical therapies that modify tau metabolism (Josephs et al., 2006b), and genetic advances (see below).

Table 2 contains a simplified summary of five neuropathological subtypes of frontotemporal lobar degeneration described by Lantos and Cairns (2001) that have been found in association with progressive language impairments. It should be noted that additional subtypes are differentiated by other authors (Josephs et al., 2006b). Some of the additional subtypes discussed by Dickson (1999) and Josephs et al. (2006b) are discussed in the footnotes to Table 2.

**PROGRESS IN RELATING CLINICAL SYNDROME TO NEUROPATHOLOGY**

As recently as 2001, researchers were cautious about proposing links between clinical presentations and likely neuropathological subtype (Hodges & Miller, 2001; McKhann et al., 2001) because there was no clear pattern to the range of clinical presentations and the neuropathology results post-mortem. More recently still, however, a small number of studies have begun to suggest that some clinical
### Pathological subtypes of frontotemporal lobar degeneration described by Lantos and Cairns (2001), with notes on additional subtypes described by other researchers

<table>
<thead>
<tr>
<th>Lantos &amp; Cairns (2001) pathological subtype</th>
<th>Description and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profile 1: Pick bodies</td>
<td>Spherical inclusions called <em>Pick bodies</em>, positive for both tau and ubiquitin.</td>
</tr>
<tr>
<td>Profile 2: Corticobasal degeneration (CBD)-type inclusions</td>
<td>Tau-positive inclusions as well as ballooned neurons (neurons that are colourless and swollen, also called Pick cells; Dickson, 2001) primarily in the cortex (Dickson, 1999), and other tau-positive inclusions in the glia (the cells that support and protect the neurons) (Hodges et al., 2003; Lantos &amp; Cairns, 2001; McKhann et al., 2001).</td>
</tr>
<tr>
<td>Profile 3: motor neuron disease (MND)b-type inclusions</td>
<td>Inclusions are tau-negative but ubiquitin-positive. This pathology may or may not be associated with clinical motor signs.</td>
</tr>
<tr>
<td>Profile 4: Dementia lacking distinct histology (DLDH)d</td>
<td>Tests negative for the inclusions described above, and shows no ballooned Pick cells. There is focal atrophy of frontal and/or temporal regions and, typically, spongiform change (brain tissue takes on appearance of a sponge).</td>
</tr>
<tr>
<td>Profile 5: frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)</td>
<td>Inclusions similar to Pick bodies, CBD-type and PSP-type inclusions. Genetic testing shows mutation in the tau gene or progranulin gene on chromosome 17 (see text).</td>
</tr>
</tbody>
</table>

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*aAlthough corticobasal degeneration neuropathology has been found in people with progressive language impairments, it is more commonly associated with a clinical motor syndrome, the symptoms of which include limb apraxia, rigidity, and dystonia (Dickson, 1999). Both the clinical syndrome and neuropathology are typically referred to as corticobasal degeneration, although recently some authors have made the distinction by referring to corticobasal degeneration (or CBD-like) syndrome (Josephs et al., 2006b; Kertesz et al., 2005). Corticobasal degeneration inclusions have a similar protein structure but a different shape and location to the inclusions found in another motor syndrome known as progressive supranuclear palsy (PSP) (Dickson, 1999). Progressive supranuclear palsy is a syndrome usually characterised by falls, gait disturbance, and difficulty with vertical eye movements (Dickson, 1999), however on some occasions pseudosupranuclear palsy-type neuropathology has been found in people with progressive language impairments (Josephs et al., 2006a, 2006b; Knibb et al., 2006). |

*bA class of diseases, the most common of which is known as amyotrophic lateral sclerosis (ALS) in North America and continental Europe (Bak, O’Donovan, Xuereb, Boniface, & Hodges, 2001). |

*cWhen the person shows neurological signs characteristic of upper or lower MND at presentation or with disease progression, along with other language or behaviour symptoms associated with frontotemporal dementia, these inclusions are almost always found at autopsy (Josephs et al., 2006b). However, when these inclusions are found in people who showed no clinical features of MND at any time during disease progression (e.g., as in many cases of semantic dementia; Davies et al., 2005), the inclusions are found in frontal and temporal cortex and the dentate gyrus of the hippocampus (Whitwell et al., 2005), rather than the lower motor neurons of the brain stem and spinal cord as typical in classic MND. NB: The spinal cord may not be examined post-mortem in the absence of motor symptoms (Mackenzie & Feldman, 2005), so these inclusions may be present in lower motor neurons but not detected. Josephs et al. (2006b) make a helpful distinction between the neuropathology associated with positive MND signs (which they call frontotemporal lobar degeneration with motor neuron disease, or FTLD-MND) and the neuropathology with no MND signs but MND-type inclusions (which they call frontotemporal lobar degeneration with ubiquitin-only immunoreactive neuronal changes, or FTLD-U). Other terms also identifying the relationship of this frontotemporal lobar degeneration neuropathological profile to the pathology found in MND include frontotemporal dementia-motor neuron disease (FTD-MND; Knibb et al., 2006) and motor neuron disease inclusion dementia (Davies et al., 2005; Jackson, Lennox, & Lowe, 1996). |

*dAlso reported as frontal-lobe degeneration-type (FLD) neuropathology (Neary, 1999), dementia lacking distinct histopathological features, or simply frontotemporal lobar degeneration (McKhann et al., 2001). |

*eProbably some cases reported as DLDH had MND-type inclusions (Profile 3) that were not detected because the test for ubiquitin was not carried out (Josephs et al., 2006a; Kertesz et al., 2005), and/or because the spinal cord was not examined (Mackenzie & Feldman, 2005).
presentations are more reliably associated with some neuropathologies than others (Davies et al., 2005; Hodges et al., 2004; Josephs et al., 2006a, 2006b; Kertesz et al., 2005; Knibb et al., 2006). Progress in this area is made possible by cases that are followed longitudinally with detailed clinical testing together with brain donation for post-mortem analysis of neuropathology. The rapid progress in this area over the past decade is likely to continue in the medium term at least.

Primary progressive aphasia

Using the Mesulam (1987) criteria for primary progressive aphasia, Kertesz et al. (2005) reported neuropathology for 22 people diagnosed with anomic, logopenic, or non-fluent primary progressive aphasia as described above, or “possible primary progressive aphasia” (so-named because memory difficulties were noted in the history over and above the aphasia that was prominent by the time of initial clinical examination). All but 1 of the 10 “possible primary progressive aphasia” cases had Alzheimer-type neuropathology, and most (90%) did not develop second or third syndromes. Of the 12 other primary progressive aphasia cases, the majority (92%) did develop behavioural or motor second syndromes, and the neuropathologies were corticobasal degeneration inclusions (5/12), frontaltemporal lobar degeneration with motor neuron disease-type inclusions (4/12), and Pick body neuropathology (3/12).

Semantic dementia

A study combining cases from Sydney and Cambridge (Davies et al., 2005) over a 10-year period found that 13/18 cases (72%) with the clinical syndrome of semantic dementia following the Lund criteria (Neary, 1999) had frontotemporal lobar degeneration with motor neuron disease-type inclusions at autopsy. Only 1 of these 13 showed symptoms of motor neuron disease during life. Of the remaining five semantic dementia cases, three had Pick body neuropathology and two had Alzheimer’s disease. Neuropathological results for people with semantic dementia in the Kertesz et al. (2005) cohort are not yet available.

Progressive non-fluent aphasia and apraxia of speech

In another Sydney/Cambridge study, 6/8 (75%) people with non-fluent progressive aphasia diagnosed by “disrupted speech output with phonological and/or syntactic errors” had Pick body neuropathology (Hodges et al., 2004). A report of 13 people with non-fluent progressive aphasia diagnosed on the basis of a prominent non-fluent aphasia “with hesitancy and phonetic errors” (Josephs et al., 2006b, p. 42) found that one had Pick body neuropathology, three had frontotemporal lobar degeneration with ubiquitin-only immunoreactive neuronal changes (FTLD-U), five had pseudo-supranuclear palsy-type neuropathology, and four had corticobasal degeneration-type neuropathology. Both these papers have been followed up by studies described below that pay more stringent attention to participants’ clinical symptoms, and the results are promising for identifying neuropathology on the basis of clinical syndrome. Taken together, 16 of the 21 (76%) nonfluent cases reported by Hodges et al. (2004) and Josephs et al. (2006b) had tau-positive neuropathology.

Knibb et al. (2006) carried out a cluster analysis of measures of language deficits in 38 people with progressive language impairments. They identified 23 broadly
non-fluent cases that could be further subdivided into two groups along lines similar to those proposed by Gorno-Tempini et al. (2004): a non-fluent progressive aphasia group \( (n = 14) \) and a logopenic progressive aphasia group \( (n = 7) \). Of the non-fluent progressive aphasia group, seven had Alzheimer’s disease neuropathology and seven had one of the tauopathies (which ones and how many of each are not specified). Of the seven logopenic cases, three had progressive supranuclear palsy-type neuropathology, three had frontotemporal lobar degeneration with motor neuron disease-type inclusions, and the pathology for the final case was not given.

Josephs et al. (2006a) considered whether or not participants had apraxia of speech: 17 individuals with progressive apraxia of speech (diagnosed as described above) and/or aphasia could be further classified according to (i) whether apraxia of speech was the sole or dominant feature in the early years after presentation (the AOS group), (ii) whether they had agrammatic or telegraphic speech as well as apraxia of speech (a group Josephs and colleagues called progressive non-fluent aphasia – apraxia of speech, PNFA-AOS), or (iii) whether they had aphasic symptoms without agrammatic or telegraphic speech (a group called primary progressive aphasia not otherwise specified). Of the apraxia of speech group, five out of seven had progressive supranuclear palsy-type neuropathology, one had corticobasal degeneration-type neuropathology, and one Pick body neuropathology. Of the PNFA-AOS group, all three had corticobasal degeneration-type neuropathology. In the primary progressive aphasia not otherwise specified group, five of seven had frontotemporal lobar degeneration with motor neuron disease-type inclusions, one had corticobasal degeneration-type neuropathology, and one progressive supranuclear palsy-type neuropathology. In this latter case, indications of mild apraxia of speech had been present at onset. Thus the major contribution of this study was to show that 11 out of 11 participants with any hint of apraxia of speech showed tau-positive neuropathology. However, a report of apraxia of speech is unlikely to predict tauopathy with 100% reliability in clinical practice, given the inconsistent criteria used across clinical and research groups to diagnose apraxia of speech (Croot, 2002), and the finding of Alzheimer-type neuropathology in a proportion of individuals who made articulatory/phonological errors in other studies (Croot, Hodges, Xuereb & Patterson., 2000; Knibb et al., 2006).

Summary of current findings on neuropathology

People who had a clinical syndrome of semantic dementia, or who were anomic without agrammatism or phonological errors, have most often been reported with frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U Davies et al., 2005; Josephs et al., 2006a; Knibb et al., 2006). This neuropathology is rarely found when phonological errors and/or apraxia of speech are prominent. Where apraxia of speech is present, the neuropathology is most often one of the tauopathies (i.e., Pick bodies, corticobasal degeneration, or progressive-supranuclear palsy neuropathology). Kertesz et al. (2005) suggested that a tauopathy is the likely neuropathy when a movement disorder emerges as a second or third syndrome after the onset of primary progressive aphasia. Hodges et al. (2003) suggest that a tauopathy is more likely in people who are older, with a slower onset and a non-fluent profile.

Finally, Alzheimer’s disease cannot be ruled out as a potential neuropathological diagnosis in either fluent or non-fluent progressive language impairments, including
semantic dementia (Davies et al., 2005; Knibb et al., 2006). In the Knibb et al. (2006) study of 38 individuals, approximately one third of those with fluent progressive aphasia and one third of those with non-fluent progressive aphasia proved to have Alzheimer-type neuropathology. Alzheimer’s disease may be identifiable by early memory difficulties (as suggested by Kertesz et al., 2005). Caution is required here, however, as memory difficulties at presentation do not reliably indicate Alzheimer’s disease neuropathology (A. J. Graham et al., 2005; Hodges et al., 2004). At least some people with progressive aphasia caused by non-Alzheimer neuropathology exhibit mild memory difficulties (Knibb et al., 2006), and some people with autopsy-confirmed Alzheimer’s disease do not show prominent episodic memory deficits at presentation (Galton et al., 2000). At this point in time, the above conclusions about the neuropathological process associated with the various subtypes of progressive aphasia are preliminary, as they are based on a small number of studies (Kertesz et al., 2005). Consequently, the use of diagnostic labels that presume a particular neuropathology would still be premature.

GENETIC DISCOVERIES

In some families the frontotemporal dementia is strongly heritable, with an autosomal dominant pattern of inheritance (50% likelihood of inheritance by male and female offspring). This subtype is known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) because of the Parkinsonian symptoms that are frequently part of the syndrome2 and because of the abnormalities found in a region of Chromosome 17 in individuals with this subtype (Lantos & Cairns, 2001). Families with FTDP-17 with tau-positive pathology have been found to have a mutation on the gene for tau that is located on this chromosome (Hutton et al., 1998). Families with ubiquitin-positive pathology have recently been shown to have a different mutation at a nearby location on Chromosome 17, a mutation affecting the gene that controls expression of progranulin, a growth factor associated with neuronal health (Baker et al., 2006). Rowland (2006) notes this as a major genetic advance, opening the way for the development of genetic therapies.

PROGNOSIS FOR PEOPLE WITH PROGRESSIVE LANGUAGE IMPAIRMENTS

As the above review would suggest, many subtle (and not-so-subtle) differences are possible between individuals with progressive language impairments. Individuals differ in the initial speech or language symptoms present, the speech or language symptoms that appear with disease progression, and the non-speech/non-language symptoms that appear over time. More than 100 single cases or small case series have been published, typically with the aim of bringing to the attention of the clinical research community a previously unreported clinical syndrome (Kertesz et al., 2003), and such reports demonstrate that these disorders are clinically heterogeneous. However, how much information is available about the specific longitudinal course(s) likely to be associated with various clinical presentations? The best

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2 The symptoms typically seen in Parkinson’s disease, including tremor, slow movements, decreased facial expression, rigidity, and postural instability (Oertel & Quinn, 1996).
information can be drawn from comparatively large group studies that used (fairly) consistent evaluations to follow participants over time (Davies et al., 2005; Hodges et al., 2003; Josephs et al., 2006a; Kertesz et al., 2003, 2005; Knibb et al., 2006; Le Rhun, Richard, & Pasquier, 2005).

Survival and autonomy

Age at onset (time when symptoms were first noticed) and duration of illness (calculated from onset until death) reported in a number of large longitudinal studies of individuals with progressive language impairments are summarised in Table 3. The typical cause of death in Alzheimer’s disease and frontotemporal dementia is aspiration pneumonia (Lantos & Cairns, 2001; Le Rhun et al., 2005). One study (Hodges et al., 2003) found longer survival in progressive non-fluent aphasia than semantic dementia. Gender, presence of family history and age at diagnosis did not further influence survival.

Consistent with this, people with non-fluent progressive aphasia were likely to enter a care institution later than people with semantic dementia (on average 7–8 years after onset in non-fluent progressive aphasia versus 3–4 years after onset in semantic dementia; Hodges et al., 2003). In an apparent contrast, Le Rhun and colleagues reported a more benign course for people with fluent primary progressive aphasia than non-fluent primary progressive aphasia (with fluency determined by their profile on a French version of the Boston Diagnostic Aphasia Examination). However, Le Rhun and colleagues excluded people with semantic dementia from their fluent sample and only included those fluent individuals who met the Mesulam et al. criteria for primary progressive aphasia. Kertesz and colleagues have argued that people with fluent aphasia meeting the Mesulam et al. criteria are likely to be earlier in the course of the disease than people with a non-fluent language profile (Kertesz et al., 2003), which would explain the better prognosis for the fluent group in the Le Rhun et al. study.

Le Rhun et al. (2005) evaluated the possibility (Mesulam, 1987) that the course of primary progressive aphasia is more benign than Alzheimer-type dementia. Their study found that survival was actually shorter for people with primary progressive aphasia than people with Alzheimer-type dementia (consistent with the findings of Hodges et al., 2003), but that autonomy in activities of daily living was preserved longer in PPA. Loss of autonomy occurred at a median of 6–7 years post-onset and 1–2 years before death in people with primary progressive aphasia. Half the participants with primary progressive aphasia were autonomous with regard to toileting, personal hygiene, and dressing at 5 years post-onset, whereas half required assistance. By 7 to 8 years after onset, half were mute and half required assistance in eating and walking. Age at onset, gender, educational level, and vascular risk factors did not influence participants’ likelihood of maintaining autonomy. In a comparison between semantic dementia and Alzheimer-type dementia, survival was found to be similar in both syndromes (Roberson et al., 2005), and gender, education, family history, and neuropsychiatric profile did not influence survival in semantic dementia.

Behaviour and personality change

Although speech and/or language impairments are most prominent in these disorders by definition, a high proportion of people also develop changes in
TABLE 3
Summary of age at onset and disease duration data

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical syndrome(s)</th>
<th>Number of participants</th>
<th>Number of Males: Females</th>
<th>Age at onset (years)</th>
<th>Disease duration from onset to death (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
</tr>
<tr>
<td>Kertesz et al. (2003)</td>
<td>PPA</td>
<td>67</td>
<td>27:40</td>
<td>66.7 (7.9)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>PPA (FTLD neuropathology)</td>
<td>12</td>
<td>6:6</td>
<td>63.8 (8.3)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>PPA (AD neuropathology)</td>
<td>10</td>
<td>5:5</td>
<td>63.1 (10.3)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>PPA (Total)</td>
<td>22</td>
<td>11:11</td>
<td>63.8 (8.3)</td>
<td>–</td>
</tr>
<tr>
<td>Le Rhun et al. (2005)</td>
<td>PPA</td>
<td>49</td>
<td>21:28</td>
<td>–</td>
<td>62</td>
</tr>
<tr>
<td>Davies et al. (2005)</td>
<td>Semantic dementia</td>
<td>18</td>
<td>10:8</td>
<td>58.3 (7.0)</td>
<td>–</td>
</tr>
<tr>
<td>Hodges et al. (2003)</td>
<td>Semantic dementia</td>
<td>9</td>
<td>6:3</td>
<td>59.4 (8.6)</td>
<td>–</td>
</tr>
<tr>
<td>Knibb et al. (2006)</td>
<td>PNFA</td>
<td>8</td>
<td>2:6</td>
<td>63.3 (5.1)</td>
<td>–</td>
</tr>
<tr>
<td>Josephs et al. (2006a)</td>
<td>AOS, AOS-PNFA, and PPA-NOS</td>
<td>17</td>
<td>8:9</td>
<td>63.8 (8.0)</td>
<td>–</td>
</tr>
</tbody>
</table>

PPA = primary progressive aphasia (Mesulam group criteria); PNFA = progressive non-fluent aphasia; AOS = apraxia of speech; AOS-PNFA = apraxia of speech with progressive non-fluent aphasia; PPA-NOS = primary progressive aphasia not otherwise specified; FTLD = frontotemporal lobar degeneration; * = for the 25 participants who died; † = for the 36 participants who died.
behaviour, personality, and social cognition. Chow, Miller, Boone, Mishkin and Cummings (2002) reported that for 30 people with the language presentations associated with frontotemporal dementia following the Lund and consensus criteria (McKhann et al., 2001; Neary, 1999; The Lund and Manchester Groups, 1994), three out of four showed neuropsychiatric symptoms or behavioural change. Participants were at various stages of disease progression in this study. Depression, apathy, and disinhibition were the most common symptoms. One third of participants showed depressed symptoms at onset, and just over 50% showed apathy and/or disinhibition at time of study. Participants who went on to demonstrate severe behaviour disturbance tended to already show behaviour changes early in progression. A similar proportion was reported by Kertesz et al. (2005), with 10/22 (46%) individuals with primary progressive aphasia (Mesulam 2001 criteria) developing behavioural difficulties as a second or third syndrome. Garrard and Hodges (1999) also observed that behaviour, personality, and social cognition changes commonly emerged during the progression of semantic dementia for a series of 20 cases. Especially common were fixations with particular types of food and time, and the hyperorality and sexual disinhibition frequently described as Klüver Bucy syndrome.

Motor disorders

Kertesz et al. (2005) found that 9 of 22 participants initially diagnosed with primary progressive aphasia developed clinical symptoms of corticobasal degeneration or pseudosupranuclear palsy as a second or third syndrome. Joseph et al.’s (2006a) study that subdivided participants according to whether they had apraxia of speech indicated that early apraxia of speech is predictive of a subsequent movement disorder. One individual in each of their subgroups (progressive apraxia of speech, primary progressive aphasia with apraxia of speech, and primary progressive aphasia without apraxia of speech) had motor features on initial clinical examination. In both groups with apraxia of speech, however, most individuals (six out of eight) with no initial movement disorder developed one or more of supranuclear gaze palsy, limb apraxia, rigidity, or bradykinesia when followed longitudinally. By contrast, in the primary progressive aphasia group without apraxia of speech, only one of the five who had no movement features at onset went on to develop a movement disorder. Motor neuron signs are less common with progression if not present initially. Johnson et al. (2005) found that approximately 3% of 153 people diagnosed with semantic dementia or non-fluent progressive aphasia at various stages of severity according to the Neary et al. (1998) criteria had developed symptoms of motor neuron disease at the time their study was carried out.

Factors associated with good or poor prognosis

One factor hypothesised to be associated with better prognosis in these studies included higher MMSE score at first visit (Le Rhun et al., 2005) potentially associated with milder language impairment and thus earlier stage of disease. Tau-positive neuropathology (Hodges et al., 2003; Roberson et al., 2005) is another, with tauopathies suggested to cause a slower rate of progression than the other neuropathologies in frontotemporal lobar degeneration (i.e., frontotemporal lobar degeneration with ubiquitin-positive inclusions or dementia lacking distinct histological
features). However, this claim requires further research, as Kertesz et al. (2005) and Knibb et al. (2006) did not find longer survival for the tau-positive cases in their studies. Josephs et al. (2006b) found longer survival for people with tau-positive neuropathology, but noted that this was due to the very short disease duration for people with frontotemporal lobar degeneration and motor neuron disease in the tau-negative group. Josephs et al. (2006b) also found longer survival for the people with Pick body neuropathology than for people with pseudosupranuclear palsy-type and corticobasal-type neuropathology, attributing this to the higher level of brainstem neuropathology and thus aspiration risk in the latter two groups.

Factors associated with poor prognosis included the development of motor neuron disease features (Kertesz et al., 2005; Roberson et al., 2005), swallowing difficulty (Kertesz et al., 2003, 2005) and immobility (Kertesz et al., 2005), as well as relatively poor performance on a letter fluency task (Roberson et al., 2005).

**CONCLUDING COMMENTS**

As the above review shows, knowledge about the clinical presentations and neuropathologies associated with progressive language impairments, and information about prognosis, has increased substantially since Mesulam (1982) introduced the term “primary progressive aphasia” a quarter of a century ago. The range of classification systems that have developed since then emphasise how important it is to specify the criteria used to reach a particular diagnosis, and the clinical symptoms on which this diagnosis is based.

Frontier areas of research into progressive language impairments include pharmacological therapies (Burns & O’Brien, 2006; Huey, Putnam, & Grafman, 2006; McNeil et al., 1995; Reed, Johnson, Thompson, Weinstaub, & Mesulam, 2004), early diagnostic indicators (Grossman et al., 2005) and genetics (Bertram & Tanzi, 2005; Blacker & Lovestone, 2006), ensuring that our knowledge of these disorders will continue to increase for many years to come. Given the emerging role of speech pathologists, psychologists, and other health professionals in assessment, education, intervention, advocacy, and policy development related to progressive language impairments (Croot et al., 2008 this issue; Taylor et al., 2008 this issue), it will be essential to follow the ongoing and rapid developments in clinicopathological diagnosis and treatment of these disorders. As pharmacological or other treatments become available to target the neuropathological mechanisms in these diseases, a primary diagnostic goal will be to identify the likely neuropathology to match clients to appropriate therapies at the earliest opportunity.

**REFERENCES**


