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Linguistic Aspects of Primary Progressive Aphasia

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Abstract

Primary progressive aphasia (PPA) refers to a disorder of declining language associated with neurodegenerative diseases such as frontotemporal degeneration and Alzheimer disease. Variants of PPA are important to recognize from a medical perspective because these syndromes are clinical markers suggesting specific underlying pathology. In this review, I discuss linguistic aspects of PPA syndromes that may prove informative for parsing our language mechanism and identifying the neural representation of fundamental elements of language. I focus on the representation of word meaning in a discussion of semantic variant PPA, grammatical comprehension and expression in a discussion of nonfluent/agrammatic variant PPA, the supporting role of short-term memory in a discussion of logopenic variant PPA, and components of language associated with discourse in a discussion of behavioral variant frontotemporal dementia. PPA provides a novel perspective that uniquely addresses facets of language and its disorders while complementing traditional aphasia syndromes that follow stroke.

Keywords

primary progressive aphasia; semantic; agrammatic; discourse; frontotemporal dementia

1. INTRODUCTION

Why should linguists consider studies of language from the perspective of aphasia? A cognitive theory can have an elegant organization that is exquisitely consistent within itself. One example is Freudian psychodynamic theory, which has provided valuable insights into human emotional behavior. But is it true? Confidence in the answer to this question would come in part from independent, converging evidence provided by a source that is minimally related to that serving as the basis of the original theory. Freudian theory has not confidently withstood the test of time because little evidence has been forthcoming from studies by an independent source. One obvious source is observations from the consequences of brain damage, in which focal disease interfering with the hypothesized neural basis of psychodynamic theory could result in a condition that closely resembles a human emotional state posited by psychodynamic theory, such as psychosis. This has not been observed. From this perspective, linguistic theory predicts specific components of a language system, and

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careful studies of aphasia could reveal impairments of these components and thus provide independent, converging evidence consistent with linguistic theory. In fact, there appear to be several important aspects of linguistic theory that are supported by studies of aphasia. It can be argued that linguistic characteristics consistent with aphasia should be pursued as central tenets because they are validated by the consequences of focal damage to the cerebrum.

And why should we consider rare conditions like the progressive aphasia instead of the more familiar aphasia that occur following a stroke? First, the location of a stroke is determined by a disorder of the cerebrovascular system, and the system for delivering blood to the brain is not organized to highlight or prioritize the neuroanatomic basis of language. Other brain regions that are less susceptible to focal stroke play an essential role in language, but the contribution of these brain regions was largely unknown until we became more aware of them by paying closer attention to the brain regions associated with the progressive aphasia. Second, a stroke indiscriminately damages both gray matter (GM) regions of the brain that contain neurons and nearby white matter (WM) regions that contain projections integrating several GM regions into a functional network. Because of the nature of the severe damage caused by a stroke, it is very difficult to determine the relative contributions of GM processing regions and WM projections in an observed language disorder. Defining the GM regions and WM regions contributing to a language disorder in a neurodegenerative condition causing a progressive aphasia is much easier because the physical damage is not nearly as destructive as it is following a stroke and thus can be defined in detail with a microscope (e.g., Giannini et al. 2017, Mesulam et al. 2014b).

Moreover, at another level, the study of primary progressive aphasia (PPA) can help inform our understanding of the genetic basis of language. Rare families have been identified with a genetic basis for an apparent language disorder (e.g., Vargha-Khadam et al. 2005). By comparison, PPA is associated with a neurodegenerative disease that appears to be familial in approximately 20% of cases, and a specific genetic mutation has been identified in approximately 80% of these cases (Wood et al. 2013). Mutations of microtubule-associated protein tau (*MAPT*), granulin (*GRN*), and other, rare autosomal dominant mutations, as well as repeat expansions of *C9orf72*, can result in progressive disorders that include language and other aspects of cognition. While these are not “pure” linguistic disorders that can distinguish *Homo sapiens* from subhuman primates, these genetic disorders appear to provide intriguing hints about the genetic basis for some components of language.

What is aphasia? Aphasia is a central disorder of language comprehension and expression. The diagnosis of aphasia requires the exclusion of peripheral sensory deficits, such as reduced auditory acuity, and peripheral motor deficits, such as weakness of the muscles of articulation, which may mimic aphasia. PPA refers to a family of understudied focal neurodegenerative syndromes primarily affecting language. “Primary” refers to the absence of obvious structural brain abnormalities, including the absence of stroke, space-occupying lesion, or head trauma; “progressive” refers to the gradual worsening of the language deficit. An early illustration of PPA was provided by Pick (1892), who described a woman with a social disorder involving disinhibition and poor insight. Her speech capacity gradually worsened and she became mute. The first report of isolated language decline came a year

later, when Srieux (1893) described a patient with worsening speech fluency without accompanying memory, social, or visuospatial impairment. In the modern literature, Mesulam (1982) reported several cases of slowly progressive aphasia. Although no obvious structural abnormality was evident in these cases, a positron emission tomography (PET) scan of brain functioning revealed reduced glucose uptake in the left hemisphere (Chawluk et al. 1986).

The diagnosis of PPA depends on the presence of a language impairment that is the primary cognitive deficit after symptom onset (Mesulam 2003, Mesulam et al. 2012). The language deficit must be insidiously progressive in nature without an identifiable cause, which rules out non-neurodegenerative etiologies such as stroke, head trauma, and space-occupying lesion. Language difficulty should be the primary impairment for some time, typically 1 to 2 years, with minimal memory, visuospatial, executive, or social difficulty observed during the early course of the disease, thereby eliminating more common neurodegenerative conditions such as typical amnesic Alzheimer disease (AD). There are no community-based surveys documenting the frequency of PPA in the population. Nevertheless, PPA is not uncommon. A rough estimate of the frequency of PPA, based on autopsy, is that approximately 40% of cases of frontotemporal lobar degeneration (FTLD) spectrum pathology have PPA (Grossman et al. 2008b, Hodges et al. 2004), suggests a prevalence in the range of 1.1–6 per 100,000 and an incidence of approximately 0.88–1.4 per 100,000. The average age of onset tends to be in the late fifties, although a wide range of ages has been reported, and we are only beginning to learn about the factors contributing to this substantial variability (Massimo et al. 2015). Survival is approximately 7 years, although there are widely varying estimates of prognosis (Hodges et al. 2003, Xie et al. 2008).

This review focuses on two subtypes of PPA with distinct linguistic phenotypes: (a) semantic variant PPA (svPPA), also known as semantic dementia or PPA-S, which is associated with a disorder of word meaning; and (b) nonfluent/agrammatic variant PPA (naPPA), also known as progressive nonfluent aphasia or PPA-G, which is associated with an impairment of grammatical processing. From a linguistic perspective, these syndromes appear to reflect disorders of specific components of a language representation and processing system that are associated with disease in discrete neuroanatomic distributions. Thus, this research provides some independent evidence supporting the nature of these fundamental components of the language network. From a clinical perspective, it is important to recognize these syndromes because they may be markers of a statistically increased risk of a specific form of FTLD pathology (Deramecourt et al. 2010, Grossman 2010, Josephs et al. 2011, Snowden et al. 2011). In an era of disease-modifying therapies, valid and reliable characterizations of PPA variants can serve as inexpensive screening tools to assess eligibility for treatment trials and help identify endpoints reflecting response to a therapeutic intervention, and linguistic characterizations can enhance these goals.

I also discuss language disorders associated with the logopenic variant of PPA (lvPPA) and the behavioral variant of frontotemporal degeneration (bvFTD). Although not associated with a narrowly defined linguistic deficit, these disorders appear to interfere with language use in the real world. Key features of lvPPA include lexical retrieval deficits during the course of conversational speech and limited auditory–verbal short-term memory (Gorno-

Tempini et al. 2004). These impairments appear to affect sentence processing during comprehension and expression. bvFTD is associated primarily with a disorder of behavior and personality as well as executive dysfunction (Rascovsky et al. 2011). Although there is no obvious aphasic disorder in bvFTD, there appear to be subtle impairments in speech, lexical semantic memory, processing of complex sentences, and especially difficulty with conversational discourse that can interfere with communication in the real world.

2. SEMANTIC VARIANT PRIMARY PROGRESSIVE APHASIA

2.1. Clinical Features

The meaning of the words we use depends on our long-term conceptual or semantic memory—our knowledge of objects, actions, ideas, and the like. Long-term memory for concepts represented in semantic memory appears to be compromised in svPPA, also known as semantic dementia. This syndrome was first described by Warrington (1975) and Snowden et al. (1989). The most common pathology in svPPA is FTLD-TDP, which is associated with the accumulation of transactive response DNA-binding protein of ~43 kD (TDP-43), an RNA-binding protein that functions normally in the nucleus to help regulate DNA and RNA processing. Patients with svPPA frequently have TDP-43 pathology (Hodges & Patterson 2007, Snowden et al. 2007). Some forms of stroke and closed-head trauma may resemble svPPA, but these are easily distinguished because of their sudden onset and nonprogressive nature. Other causes of a pattern of semantic memory difficulty resembling svPPA include herpes encephalitis (Lambon Ralph et al. 2007, Noppeney et al. 2007, Patterson et al. 2015), but this is often subacute in progression and associated with the stigma of an infection.

Clinical research consensus criteria for svPPA focus on two essential features (Gorno-Tempini et al. 2011), with reliable and widely accepted recognition of this syndrome (Mesulam et al. 2012, Sajjadi et al. 2012). The first is profound confrontation naming difficulty (Hodges & Patterson 2007, Patterson et al. 2007). Thus, these patients' ability to name pictured objects or use these words in spontaneous speech is quite impaired. Analyses of naming errors suggest that patients with svPPA may substitute the name of a prototype, or a more frequent and familiar object that shares many of the same features as the target object (Patterson 2006, 2007). They may also substitute a more general, superordinate term when a basic-level name of a specific object is difficult to retrieve (Hodges et al. 1995, Hoffman et al. 2013). When asked to name a picture of a camel, for example, svPPA patients may substitute 'horse' or 'animal.' Even superordinate terms become difficult for these patients over time, and as the disease progresses, the meaningfulness of words becomes increasingly vague and ultimately consists of terms like 'that' and 'thing.'

The second major clinical feature is impaired comprehension of single words (Patterson et al. 2007). Thus, the ability of patients with svPPA to understand basic-level object names is highly impaired. Over time, this impairment appears to extend to difficulty understanding superordinate terms, paralleling the difficulty in language expression. This deficit at the single-word level understandably has a significant impact on sentences as well. Patients with svPPA thus appear to be impaired on tasks that involve sentence comprehension (Charles et al. 2014) and sentence expression (Ash et al. 2013).

Because there seems to be a problem in comprehension and expression that interferes with the ability to understand, recognize, and name objects and single words, the core deficit in svPPA is thought to involve semantic memory (Patterson et al. 2007). There have been some controversies in specifying the precise basis of the semantic memory deficit. One challenge may be that svPPA is a progressive disorder, and the evolution of this syndrome over time has made it difficult to fully characterize this deficit. With this caveat in mind, one frequently mentioned account is that these patients have a universal, “amodal” deficit in semantic memory, wherein knowledge of every aspect of every type of concept becomes degraded. Evidence consistent with this claim has been reported in svPPA patients with selective deficits for all aspects of a category of knowledge within semantic memory, known as a category-specific deficit. Single cases and small series of cases have been reported with a deficit for concepts involving living things (e.g., animals) versus nonliving things (e.g., tools, furniture) (Carroll & Garrard 2005, Lambon Ralph et al. 2007, Libon et al. 2013, Rogers et al. 2004). The reverse pattern of impairment—greater difficulty with manufactured than natural objects—has also been described in svPPA (Cappa et al. 1998, Moss & Tyler 2000, Sacchetti & Humphreys 1992), suggesting that natural objects are not simply more difficult to name and understand than manufactured objects.

This account is consistent with Tulving’s (1972) proposed theory of human memory, in which he characterized semantic memory as a single, amodal system in which all semantic knowledge is stored. One specific proposal for an amodal semantic system is that knowledge in semantic memory may be represented in the form of propositions characterizing features of concepts, and a word or an object is said to be consistent with the concept when it meets the criteria specified by the list of associated propositions (Katz 1972). A camel, for example, might have positive features like ‘has four legs,’ ‘has one or two humps,’ ‘is tan-colored,’ and ‘lives in the desert.’ If an animal flies or has fins for swimming, it is unlikely to be a camel. Although this kind of propositional list could be selectively impaired in svPPA, there are many challenges associated with this approach to semantic memory, such as deciding what to include as qualifying and disqualifying features.

Another possibility involves a distributed model of sensory–motor feature knowledge. Most object concepts consist of several features taken from several different modalities. Thus, the concept of a camel might involve activation of associated color knowledge, activation of shape information associated with the humps of a camel, and activation of general world knowledge that a camel lives in a desert. The pattern of activation across these independent and distributed reservoirs of knowledge then would be interpreted as ‘camel.’ While collections of knowledge can be organized in many different ways, one approach is related in part to a theory of semantic memory known as embodied cognition (Barsalou 2009). The central idea is that the sensory and motor feature associations of concepts constitute the primary organizing principle in semantic memory, which is consistent with the theory that sensory–feature dimensions can provide insight into the structure of the semantic system and the knowledge underlying concepts represented in semantic memory [Hume 1778 (1739)]. From this perspective, the pattern of impairment in svPPA may be related in part to degradation of these multimodal reservoirs of knowledge contributing to concepts. In addition to difficulty naming pictures of objects and judging associations between pictured objects and their names, patients with svPPA are said to have deficits that extend to other

modalities such as object use (Bozeat 2000, Corbett et al. 2015, Jurkowski 1976, Silveri & Ciccarelli 2009) and environmental sounds (Binney et al. 2010). However, embodied cognition does not appear to fully explain semantic representations of conceptual knowledge (Caramazza et al. 2014, Chatterjee 2014).

Another possibility, called the hub-and-spoke model (Patterson et al. 2007), suggests that modality-specific feature knowledge about object concepts is conveyed by “spokes” to a coordinating “hub” where the concept emerges. Although sensory–motor feature knowledge may be distributed, this organizing element helps coordinate the various components of knowledge that contribute to a meaningful concept in semantic memory. In svPPA, from this perspective, it is the coordinating hub rather than representations of knowledge that is compromised, resulting in an “amodal” deficit in semantic memory. This approach has been examined in recent studies of svPPA (Lambon Ralph et al. 2017). However, these clinical and experimental observations have overwhelmingly involved materials that are depicted visually. Even when target materials are presented in a nonvisual modality, such as auditory presentation of environmental sounds (e.g., the clanging of a bell) or manual presentation of objects (e.g., the feel of a rabbit’s fur), the concepts being probed by the presented materials are overwhelmingly visually based and the task often depends on visual materials (e.g., matching the sound of a bell to a picture of a bell). It is important in this context to make the subtle distinction between the modality for depicting a concept and the nature of the knowledge essential to a concept’s meaning. Thus, even though the feel of a rabbit’s fur may be a tactile sensation, the concept of ‘rabbitness’ is fundamentally visual and depends on its appearance, regardless of the modality for presenting the concept.

Patients with svPPA appear to have disproportionate difficulty with concrete object concepts, where the concept depends largely on visual feature knowledge regardless of the modality used to depict the concept. These patients do not have visual agnosia, and they do not have difficulty interpreting materials presented specifically in the visual modality (e.g., difficulty understanding a picture of a bell), with preserved access to the same concepts from other modalities (e.g., preserved knowledge of a bell when presented in an auditory or haptic modality). Experimental observations thus emphasize that deficits in svPPA are related to the dependence of object concepts on the associated visual feature knowledge (Bonner et al. 2016). Many of these patients in fact show the phenomenon of “reversal of the concreteness effect,” in which patients have greater difficulty with concrete objects than abstract concepts (Bonner et al. 2009, Breedin et al. 1994, Macoir 2009, Papagno et al. 2009, Warrington 1975). Relative deficits with concrete object concepts compared with abstract concepts are found in large series of svPPA patients both in comprehension using lexical stimuli and in narrative expression (Cousins et al. 2016, 2017; Hoffman et al. 2013). Other examples of relative sensory–motor deficits include difficulty naming and understanding concepts that are associated with motor actions in nonaphasic patients with a neurodegenerative motor disorder known as amyotrophic lateral sclerosis (Grossman et al. 2008a, York et al. 2014), and reduced comprehension of concepts like ‘thunder’ that depend on auditory feature knowledge in patients who have difficulty with auditory short-term memory (Bonner & Grossman 2012). Note that, because most object concepts do not consist exclusively of visual features, object knowledge may be supported in part by features that are not visual in nature. Nevertheless, loss of the core visual feature knowledge associated with an object

concept may lead to impoverished or poorly organized nonvisual associative knowledge. For example, a bell has a characteristic shape; although representation of the concept of a bell may be partially degraded in svPPA because of impoverished visual feature knowledge, this deficit can be mitigated in part by knowledge of the clanging sound of a bell or the association of a bell with abstract knowledge of Sunday religious services. Moreover, in svPPA patients studied late in disease, the core deficit may gradually extend to other domains such as object use and environmental sounds as the disease progresses and encompasses brain regions important for the representation of auditory knowledge (see below).

An approach related to the hub-and-spoke and embodied cognition models, known as the heteromodal model of semantic memory, builds on the sensory–motor features associated with object concepts. According to the heteromodal model, feature representations in multiple sensory and motor reservoirs of knowledge together contribute to typical, multimodal concepts, which are represented in semantic networks that include a heteromodal integrative component (Beauchamp et al. 2004a,b; Price et al. 2015, 2016). Unlike the hub-and-spoke model, there is additional knowledge that is not necessarily sensory–motor in nature, and this too can be incorporated into concepts. In addition to the multiple sensory–motor attributes of a bell, such as its visual shape and auditory sound, a bell could also be associated with the concept of liberty in the United States or a Sunday religious service; the concept of a camel also includes the facts that it lives in the desert, has a circulatory system, and is not a very friendly animal. Whereas some of the semantic representation associated with a concept is derived in part from sensory–motor feature knowledge, additional information may thus be based on acquired associative knowledge that is more abstract and not necessarily sensory–motor in nature. Indeed, the heteromodal account also accommodates other concepts that are sensory–motor only weakly or not at all.

From the perspective of svPPA, it is the class of concepts that are abstract and minimally related to objects that is relatively preserved, which seems to contradict the idea that these patients have an amodal semantic deficit. One example mentioned above is the reversal of the concreteness effect, that is, the remarkable finding of inferior performance with concrete, visual words compared with abstract words (Bonner et al. 2009, Breedin et al. 1994, Cousins et al. 2016, Warrington 1975). The vocabulary of svPPA patients also loses high-imageability words during expression, and consists of significantly more abstract words (Cousins et al. 2017, Hoffman et al. 2013). svPPA patients also appear to have relatively preserved appreciation of musical meaning (Weinstein et al. 2011), although some investigators have noted difficulty with musical knowledge in music–picture matching tasks (Goll et al. 2009, 2012). Finally, svPPA patients appear to have relatively preserved knowledge of number concepts and numerosity (Cappelletti et al. 2001, Crutch & Warrington 2002, Halpern et al. 2004, Jefferies et al. 2004), although some investigators have also noted difficulty with number knowledge in svPPA patients who are quite impaired (Jefferies et al. 2005). svPPA patients also have relatively preserved knowledge of the class of words that depend on numbers, like ‘most,’ ‘less than half,’ and ‘few,’ known as quantifiers (Ash et al. 2016, Cappelletti et al. 2006). While additional research is needed to fully understand the representation of object concepts in semantic memory and the

degradation of these concepts in svPPA, these findings suggest that object concepts are particularly vulnerable in svPPA.

2.2. Anatomic Features

svPPA has a distinctive anatomic distribution of disease. Imaging studies associate this syndrome with left anterior and ventral temporal atrophy, which affects the anterior and ventral GM regions of the temporal lobe as well as the anterior hippocampus and the amygdala (Gorno-Tempini et al. 2004, Grossman et al. 2004, Rohrer et al. 2010a). There are also changes in the WM projections from this area to other brain regions, including the middle longitudinal fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus (Acosta-Cabronero et al. 2011, Agosta et al. 2010). Use of a functional imaging technique known as arterial spin labeling indicates that the disease progresses from areas of established disease to adjacent regions over time (Olm et al. 2016). Longitudinal imaging shows atrophy extending posteriorly and superiorly into the GM of the ipsilateral temporal lobe, and dorsally into the insula and the ventral frontal lobe, as well as involvement of the contralateral temporal lobe (Brambati et al. 2009, Olm et al. 2016). Disease associated with svPPA may begin in the left hemisphere, often spreading to involve the contralateral temporal lobe. Whereas some investigators emphasize the role of the left anterior temporal lobe in the semantic memory deficit of patients with svPPA (Patterson et al. 2015), some functional anatomy studies appear to implicate the atrophic anterior and ventral temporal regions of the right hemisphere in the semantic deficits of svPPA patients as well (Lambon Ralph et al. 2010a, Pobric et al. 2007).

Several studies have related difficulty with semantically mediated tasks directly to the left anterior and ventral temporal anatomic distribution of GM disease in svPPA (Bonner et al. 2016; Cousins et al. 2016, 2017; Lambon Ralph et al. 2010b; Libon et al. 2013; Mion et al. 2010). A critical feature of the semantic deficit in svPPA is difficulty with object concepts that depend on visual feature knowledge. Disease in the ventral and ventrolateral portions of the anterior temporal lobe in svPPA encompasses an extensive area of visual association cortex (Gloor 1997, Olson et al. 2007). These structures have been linked with high-level aspects of visual perception (Mundy et al. 2013, Murray et al. 2007), mental imagery (Zeidman & Maguire 2016), and high-level visual-object representation (Kravitz et al. 2013, Murray et al. 2007, Quiroga 2012). There is a functional anatomic gradient through the temporal lobe visual processing stream, with relatively elementary visual-perceptual features such as color and shape processed in posterior regions of the temporal lobe, and the association of visual-perceptual features with semantic value occurs in more anterior portions of the visual stream, including the anterior fusiform and parahippocampal gyri. Impairments of meaning for words and pictures of objects that depend on visual feature knowledge in both comprehension and expression tasks are thus associated with disease in the parahippocampal gyrus (Bonner et al. 2016; Cousins et al. 2016, 2017; Libon et al. 2013) and the adjacent anterior fusiform gyrus (Mion et al. 2010) in anterior portions of the ventral temporal lobe. This finding is consistent with extensive evidence from functional imaging studies in healthy adults showing that recognition of concepts associated with concrete words activates extensive areas associated with visual feature processing in the inferior temporal cortices, including the fusiform and parahippocampal gyri (Binder & Desai 2011,

Fairhall & Caramazza 2013, Martin 2007, Mellet et al. 1998, Mion et al. 2010, Simmons et al. 2006, Wang et al. 2010).

These findings are consistent in part with the embodiment or sensory–motor approach to semantic memory, in which the neural representation of knowledge in semantic memory is linked to areas of the brain that are important for sensory–motor processing (Martin 2007). Thus, concepts may be associated with or adjacent to the brain’s sensory and motor systems, and networks of activation in modality-specific association cortices may be recruited depending on the nature of the concept (Barsalou 2009, Hauk et al. 2004, Simmons et al. 2006). In svPPA, this recruitment is focused on the representation of visual feature knowledge that is crucial for representing the meaning of object concepts. Other examples relating sensory–motor features to concepts include activation of motor cortex for actions involving specific body parts (Hauk et al. 2004) and activation of auditory association cortex for auditory feature knowledge (Kiefer et al. 2008, 2012), gustatory cortex for appetizing foods (Simmons et al. 2005), and olfactory cortex for feature knowledge associated with smell (González et al. 2006).

As noted above, most concepts involve multiple modalities as well as general world or abstract knowledge that is not associated with a particular sensory–motor modality. Heteromodal brain regions are not associated with a specific sensory–motor feature but rather are convergence zones receiving projections from multiple sensory and motor association cortices (Pandya & Yeterian 1985). Such convergence zones may play an important role in integrating information from many modality-specific inputs. Some investigators claim that specific portions of the anterior temporal lobe, the focus of disease in svPPA, may serve as a potential convergence zone (Davies et al. 2004, Knibb et al. 2006). Other research with repetitive transcranial magnetic stimulation (rTMS) and functional magnetic resonance imaging (fMRI) has also emphasized the role of the anterior temporal lobe in word meaning (Baron & Osherson 2011; Bemis & Pykkanen 2011; Pobric et al. 2007, 2010; Visser & Lambon Ralph 2011). However, the multimodal nature of the ventral temporal lobe has not been confirmed by others (Bonner et al. 2013, Price et al. 2015). The superior temporal gyrus in fact is associated with auditory processing and is thought to be composed of auditory association cortex, whereas the inferior temporal gyrus and ventral temporal regions are visual association cortices; a visual–auditory convergence zone can be found in the middle temporal gyrus and the adjacent sulci. From this perspective, disease beginning in the anterior and ventral portions of the temporal lobe of svPPA may spread over time and increasingly result in a multimodal deficit as it involves auditory association cortex.

Studies of svPPA also have shown WM disease, including reduced fractional anisotropy (FA) in WM projections of the anterior temporal lobe (Agosta et al. 2010, Acosta-Cabronero et al. 2011, Brambati et al. 2009). Connectivity with other brain regions thus becomes compromised over time (Agosta et al. 2010, Brambati et al. 2009, Duda et al. 2008, Olm et al. 2016), which may also contribute to a multimodal semantic memory deficit in svPPA. These observations emphasize that the semantic memory deficit in svPPA is due in part to the disruption of a large-scale neural network involving multiple GM regions and WM projections, even if the anterior temporal lobe does not necessarily serve as a hub (Collins et

al. 2017). By comparison, the cytoarchitecture and WM connectivity of the angular gyrus appear to be well suited to perform heteromodal integrative functions in semantic memory (Glasser & Van Essen 2011, Jacobs et al. 2001, Orban et al. 2004). Many studies have associated the angular gyrus and adjacent cortices with semantic memory (Binder & Desai 2011, Price et al. 2015). Additional research is needed to evaluate the role of multiple brain regions in disruption of the semantic memory network in svPPA.

3. NONFLUENT/AGRAMMATIC PRIMARY PROGRESSIVE APHASIA

Another form of PPA appears to be associated with the integration of words into a sentence. The characteristic feature of this disorder is effortful, nonfluent speech associated with highly simplified structures in utterances, and a corresponding deficit understanding grammatically complex utterances. This is known as the nonfluent/agrammatic variant of PPA (naPPA). The effortful nature of the speech disorder in these patients was first described by Mesulam (1982) as slowly progressive aphasia, and the distinction between the fluent speech of svPPA and the nonfluent speech of naPPA, as well as the link between this speech characteristic and the linguistic disorder of agrammatism, was subsequently encompassed by the syndrome of progressive nonfluent aphasia (Grossman et al. 1996). Some of these patients are also reported to have an articulatory disorder that results in the production of degraded speech sounds and a disordered, prolonged pattern of pauses in connected speech known as apraxia of speech (AoS) (Josephs et al. 2012, 2013b). The combination of these linguistic and speech characteristics has led to clinical research consensus criteria for the syndrome known as naPPA (Gorno-Tempini et al. 2011), and this syndrome has been widely accepted (Mesulam et al. 2012, Sajjadi et al. 2012). naPPA is often associated with FTLDTau pathology (Deramecourt et al. 2010; Grossman 2010, 2012; Josephs et al. 2011; Snowden et al. 2011), involving the accumulation of the microtubule-associated protein tau. The naPPA syndrome may resemble Broca's aphasia because of the slowed speech. However, Broca's aphasia is distinguished clinically from naPPA in that the former is associated with a hemiplegia and caused by the sudden onset of a stroke, but there is no extrapyramidal disorder or AoS.

3.1. Clinical Features

The hallmark of naPPA is effortful, nonfluent speech. Although effortful speech has been recognized clinically (Grossman et al. 1996), quantification of the slowed speech rate has been documented only recently (Ash et al. 2009, Gunawardena et al. 2010, Rogalski et al. 2011a, Wilson et al. 2010b). Speech is produced at an average rate of approximately 45 words per minute (WPM) by naPPA patients versus approximately 140 WPM by healthy, age-matched adults. Although there are many lengthy pauses in these patients' effortful speech, their speech remains significantly slowed even when pauses >2-s duration are taken into consideration (Ash et al. 2009).

Careful analyses have allowed investigators to test several hypotheses about the basis of the slowed, effortful speech found in naPPA. One essential characteristic of speech in naPPA is the disorder of its grammatical features (Ash et al. 2009, Gunawardena et al. 2010, Knibb et al. 2009, Rogalski et al. 2011a, Wilson et al. 2010b). Grammatical deficits in speech are

highly correlated with effortfulness and slowed WPM. In semistructured speech samples that involve a description of a single picture (Ash et al. 2013) or a lengthier, wordless picture story (Ash et al. 2009, Gunawardena et al. 2010), and in conversational speech (Knibb et al. 2009), quantified analyses reveal that the variety of grammatical forms is impoverished and that grammatical forms are simplified, with fewer utterances containing features like a subordinate clause or the passive voice. Grammatical simplifications also result in a shortened mean length of utterance (MLU). When syntactic features are produced, they are more likely to contain errors. Speakers may omit grammatical morphemes, including inflections and free-standing morphemes such as ‘was’ and articles like ‘a,’ and they may use inappropriate grammatical inflections.

Some naPPA patients also appear to have a motor disorder that may contribute to their effortful speech. AoS involves impaired coordination and planning of the motor articulators. Clinical characteristics of AoS are thought to include the production of incorrect speech sounds and sequences of sounds that do not occur in the speaker’s native language, searching for the correct speech sound but not necessarily producing the intended target after several attempts, and oddly placed pauses in the speech stream. These characteristics are consistent with the observation that some patients with naPPA have an extrapyramidal disorder such as progressive supranuclear palsy or corticobasal degeneration that can result in poor control of the motor speech apparatus (Josephs et al. 2006, 2012; Santos-Santos et al. 2016), although AoS can occur without any other observable motor disorder (Grossman 2012, Rohrer et al. 2010a) and without evidence of a linguistic disorder such as agrammatism (Josephs et al. 2012).

It is crucial to quantify apractic speech disorders objectively so that these observations can be reproduced reliably in other laboratories. In one attempt to quantify speech errors consistent with AoS in naPPA (Ash et al. 2010), phonetic errors involving misarticulated speech sounds that are not part of the English speech sound system were used as markers of misplaced articulators related to an impaired motor coordination system. naPPA patients were found to produce significantly more speech errors than controls, consistent with other observations (Josephs et al. 2006, Rohrer et al. 2010b). However, only 21% of speech errors in naPPA could be attributed to a motor speech planning disorder because they were distortions that are not part of the English speech sound system. In another study, the duration of syllable production was lengthened and the stress of initial versus subsequent syllable was disordered in patients with AoS compared with controls and other PPA patient groups (Duffy et al. 2017). Two classes of speech sound errors have been identified—one consisting of speech sound errors, distortions, and substitutions and the other consisting of syllabically segmented prosodic speech patterns. The former type of error was reported more commonly in naPPA, whereas the latter was found in individuals with AoS (Josephs et al. 2013b).

Patients with naPPA also have grammatical comprehension difficulty (Grossman et al. 1996, Mesulam et al. 2012), providing additional evidence that effortful speech in naPPA is not determined entirely by a motor disorder. In a sentence like ‘Boys that girls kick are unfriendly,’ for example, naPPA patients often err when asked, ‘Who did the kicking?’ (Peelle et al. 2008). These patients also have difficulty pointing to one of two pictures based

on a sentence, where selecting the correct picture depends on appreciating the sentence's grammatical structure (Charles et al. 2014, Wilson et al. 2010a). Another study used an anagram task to show that patients with naPPA have difficulty ordering words printed on cards into a grammatically complex question about a picture (Weintraub et al. 2009). Grammatical difficulties such as these may help distinguish naPPA from other PPA variants (Charles et al. 2014, Mesulam et al. 2012, Peelle et al. 2008). However, investigators must take care, as comprehension of center-embedded subordinate phrase constructions is broadly impaired across all PPA variants: These sentences are long and typically involve multiple propositions, and thus are sensitive to processing resources such as limited auditory-verbal short-term memory and working memory that may be compromised in other aphasic and nonaphasic variants of frontotemporal degeneration such as lvPPA and bvFTD. Cleft sentences are more likely to be selectively impaired in naPPA and are not significantly impaired in other patient groups, possibly because they are less confounded by greater length and larger number of propositions (Charles et al. 2014). Although nonspecific cognitive difficulty may contribute to comprehension impairments, a correlation between nonspecific measures of dementia, such as the Mini-Mental State Exam (MMSE), and comprehension performance is typically not found in naPPA. Finally, note that naPPA is a progressive disorder of language, and several studies have shown progressive decline of grammatical comprehension in naPPA (Grossman & Moore 2005, Rogalski et al. 2011b).

Measures like those described above are off-line and therefore depend in part on task-related resources like working memory and executive functioning that are needed to answer specific questions about these materials. Patients with naPPA have some working memory deficits (Libon et al. 2007, 2009), which, as noted above, may contribute to grammatical comprehension difficulty for lengthier and more complex sentences. Several investigations minimized confounding task-related resources by examining online processing of grammatical materials in sentences. One study showed slowed processing of grammatical agreements in subordinate clauses of sentences containing a prepositional phrase that elongates the gap between long-distance, syntactically dependent words (Grossman et al. 2005). This study suggested that long-distance grammatical representations in working memory are degraded in naPPA. A second online study demonstrated insensitivity to lexical grammatical category violations (e.g., a noun occurring in a verb sentential slot) but normal sensitivity to lexical semantic violations (Peelle et al. 2007).

3.2. Anatomic Features

Extensive imaging evidence suggests that a clinical marker for naPPA is focal disease centered in the left frontal lobe. Structural MRI studies emphasize GM atrophy in the inferior frontal region of the left hemisphere (Gorno-Tempini et al. 2004, Grossman et al. 1996, Peelle et al. 2008, Rohrer et al. 2011). This atrophy typically extends beyond the region in the inferior frontal lobe colloquially known as Broca's area to involve the frontal operculum and anterior insula, left prefrontal regions that are more dorsal and anterior, and superior portions of the left anterior temporal lobe (Gunawardena et al. 2010, Rogalski et al. 2011a). Structural imaging findings have been confirmed by functional imaging techniques such as positron emission tomography (PET), showing functional deficits in the left inferior frontal lobe, including the frontal operculum and the anterior insula, as well as the anterior-

superior temporal lobe (Grossman et al. 1996, Nestor et al. 2003). In patients with pure progressive AoS, GM atrophy and reduced PET glucose metabolism are found in the superior lateral premotor cortex and supplementary motor area; associated WM disease involves premotor components of the superior longitudinal fasciculus and extends into the body of the corpus callosum (Josephs et al. 2012).

Several studies have used regression analyses to link the slowed, effortful speech in these patients directly to these left frontal regions (Gunawardena et al. 2010, Rogalski et al. 2011a, Wilson et al. 2010b). Likewise, simplification of grammatical forms in semistructured speech samples have been related to GM atrophy in the inferior frontal and anterior–superior temporal regions of the left hemisphere (Gunawardena et al. 2010, Rogalski et al. 2011a, Wilson et al. 2010b). Motor speech abnormalities in patients with movement disorders such as progressive supranuclear palsy are associated with atrophy of deep GM structures such as the striatum (Santos-Santos et al. 2016).

Sentence comprehension appears to be related to regional GM atrophy in naPPA as well. Impaired sentence comprehension is associated with the posterior–inferior frontal and anterior–superior temporal regions of the left hemisphere (Pelle et al. 2008). Comprehension of cleft sentences in naPPA is related to left anterior–superior temporal GM atrophy, and GM disease in the left inferior frontal lobe is associated with difficulty understanding center-embedded sentences (Charles et al. 2014). Grammatical comprehension is related to the left inferior frontal regions in a heterogeneous group of progressive aphasics that included individuals with naPPA (Wilson et al. 2010a).

WM changes are also found in naPPA. These changes include pathways containing reciprocal projections involving the left inferior frontal lobe, such as the anterior corpus callosum, which integrates left and right inferior frontal regions; the arcuate/superior longitudinal fasciculus complex, which constitutes the so-called dorsal stream projecting between frontal and posterior–superior temporal regions; and the inferior frontal–occipital fasciculus and the inferior longitudinal fasciculus, which are part of the so-called ventral stream between the frontal and posterior temporal regions (Agosta et al. 2012, Duda et al. 2008, Galantucci et al. 2011, Schwindt et al. 2013). WM disease in naPPA also appears to involve the uncinate fasciculus, which contains projections between the inferior frontal region and the anterior temporal lobe. This finding is consistent with observations of patients with autopsy-confirmed naPPA in whom imaging revealed WM disease in the superior longitudinal fasciculus, inferior frontal–occipital fasciculus, and uncinate fasciculus (Grossman et al. 2013). Finally, WM atrophy is associated with dysarthria and motor speech abnormalities in frontal WM regions (Josephs et al. 2012, Santos-Santos et al. 2016).

Regression analyses have linked large-scale networks of disturbed anatomy directly to language deficits in naPPA. Three GM–WM networks for language expression have been identified (Grossman et al. 2013). In the first network, disease in the left inferior frontal cortex and WM disease in the anterior corpus callosum appear to be related to slowed, effortful speech. Speech errors also may be related to left frontal GM disease. In the second network, GM disease in the left frontal lobe and in the arcuate/superior longitudinal fasciculus projecting to posterior perisylvian cortical regions—the so-called dorsal stream—

is disrupted in naPPA. The dorsal stream is thought to partly mediate long-distance syntactic dependencies (Friederici 2011), and thus may contribute to deficits in grammatical expression and comprehension in naPPA that depend on long-distance syntactic dependencies. Evidence consistent with this hypothesis comes from the observation that this dorsal-stream projection appears to mediate a left frontal–parietal verbal working memory system that supports processing long-distance syntactic dependencies in sentences (Grossman et al. 2005, Peelle et al. 2008). Comprehension of cleft sentences in naPPA is associated with left anterior–superior temporal GM atrophy and WM disease in the anterior corpus callosum and corona radiata near the left superior longitudinal fasciculus (Charles et al. 2014). The third large-scale neural network that is disrupted in naPPA includes the inferior frontal–occipital fasciculus coursing through the external capsule to posterior–superior temporal regions. GM disease in the left inferior frontal lobe and WM disease in the left inferior frontal–occipital fasciculus are associated with difficulty understanding center-embedded sentences (Charles et al. 2014). This is the so-called ventral stream, which may support lexical representations important for grammatical processing, such as the major grammatical category of words and thematic roles in sentences (Hickok & Poeppel 2007).

fMRI also has been used to assess the neuroanatomic basis of grammatical processing in naPPA. Patients with naPPA do not appear to activate the inferior frontal region during comprehension of center-embedded sentences, although they recruit dorsal portions of the left frontal lobe associated with working memory and left posterior–superior temporal regions associated with language comprehension (Cooke et al. 2003). Another fMRI study showed greater left inferior frontal activation during grammatically complex sentences compared with simple sentences in controls, whereas patients with naPPA did not show a difference in left inferior frontal activation for these two types of sentences (Wilson et al. 2010a). In a more recent study, recruitment of a broad, left hemisphere language network was particularly disrupted in patients with grammatical comprehension difficulty due to naPPA (Wilson et al. 2016). Such findings suggest that the language impairment in naPPA is due in part to disruption of large-scale perisylvian neural networks that support language processing.

4. LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA

svPPA and naPPA represent the core forms of PPA that can be reliably identified (Mesulam et al. 2012, Sajjadi et al. 2012). However, there remains a large and heterogeneous group of patients with a prominent language disorder in the context of modest difficulties in other cognitive domains, thereby meeting the core criteria for PPA. In the initial description of these cases (Gorno-Tempini et al. 2004), these patients were labeled logopenic (from the Greek for ‘few words’) because a salient feature of lvPPA is impaired lexical retrieval in the course of conversational speech. A second salient feature that is an essential clinical criterion is impaired repetition of sentences and phrases (Gorno-Tempini et al. 2011). Unfortunately, the identification of patients with lvPPA has proven to be very challenging because these clinical characteristics have been identified with poor reliability (Mesulam et al. 2012, Sajjadi et al. 2012).

Much research has been directed toward developing more reliable criteria for these cases (Mesulam et al. 2012, 2014a). Doing so is important because the most common pathology underlying lvPPA appears to be AD (Grossman 2010, Giannini et al. 2017)—specifically, a nonamnesic variant of AD, because the anatomic distribution of the pathology is not initially in parts of the brain important for memory but instead is centered in neocortical portions of the temporal lobe in the left hemisphere that are related to language, such as lexical retrieval and auditory–verbal short-term memory. This is sometimes referred to as hippocampal-sparing AD (Murray et al. 2011). It is important to recognize these patients because they should be eligible for disease-modifying treatments for the pathology underlying AD despite the absence of memory deficits.

4.1. Clinical Features

Essential features of lvPPA include a deficit in repetition and difficulty with lexical retrieval in conversational speech (Gorno-Tempini et al. 2011). Following the seminal observations of Gorno-Tempini et al. (2008), the deficit in repetition was associated with a disorder of the phonological loop, a component of working memory responsible for short-term representation of auditory–verbal information (Leyton et al. 2014b). The deficits causing the language impairment thus include some difficulty with comprehension and expression of lengthy sentences, possibly related to the same impairment underlying the repetition disorder, namely limited auditory–verbal short-term memory (Ash et al. 2013, Charles et al. 2014, Gorno-Tempini et al. 2008). Likewise, speech sound errors are evident in these patients, again potentially related to overwhelmed resource demands associated with language processing in the context of a limited phonologic buffer for auditory–verbal short-term memory (Ash et al. 2013, Leyton et al. 2014a).

While these patients have some difficulty with visual confrontation naming, a particularly marked deficit has been observed in lexical retrieval during the course of conversational speech (Leyton et al. 2017). Indeed, deficits with lexical retrieval are fairly ubiquitous among all progressive aphasics; thus, criteria incorporating this impairment as a defining feature are less helpful. Finally, there are challenges associated with excluding patients on the basis of the presence of a verbal episodic memory deficit because lexical retrieval deficits can interfere with lexical retrieval needed for retrieving target words. According to the published diagnostic criteria (Gorno-Tempini et al. 2011, Mesulam 2003), verbal episodic memory should be spared. However, evaluations of verbal episodic memory have yielded inconsistent results in lvPPA (Flanagan et al. 2014, Rohrer et al. 2013). Verbal episodic memory is frequently assessed with delayed verbal free recall, in which participants name a list of recalled words after a delay period. However, recall may be confounded by the lexical retrieval deficit in lvPPA. One research group assessed both verbal and nonverbal episodic memory in PPA patients and found verbal retrieval failures compared with relatively successful visual memory (Weintraub et al. 2013). However, this group included a mixture of PPA variants (including agrammatic, logopenic, and semantic). Another study associated lexical retrieval difficulty during verbal episodic memory recall with mid-temporal atrophy in the left hemisphere, that is, the same area implicated in the confrontation naming difficulty of these patients (Win et al. 2017). A detailed examination indicated that these patients had no evidence of disease affecting parts of the brain important

for episodic memory. With these caveats in mind, I explicitly exclude patients with episodic memory difficulty from those considered to have a form of PPA (e.g., Whitwell et al. 2012), consistent with Mesulam's (2003) view that the primary deficit in patients should be a language disorder. Thus, the phenotype associated with lvPPA is not as well defined as in the other variants of PPA. Additional research is needed to determine the nature of the language deficits more reliably.

4.2. Anatomic Features

Many studies have now replicated the initial MRI observations made by Gorno-Tempini (2004) associating the lvPPA phenotype with GM atrophy in posterior perisylvian regions, including the inferior parietal lobule and posterolateral temporal GM in the left hemisphere (Rogalski et al. 2011a). Phonological short-term maintenance processes have been associated with posterior–superior temporal and inferior parietal areas, corresponding to core anatomic regions of disease in lvPPA (Gorno-Tempini et al. 2008, Rogalski et al. 2011a). This observation matches well with the primarily temporal and parietal anatomic distribution of pathology in the left hemisphere of these patients (Giannini et al. 2017, Mesulam et al. 2014b). Longitudinal imaging studies of patients with lvPPA have suggested that GM atrophy initially involving the left temporal–parietal region subsequently spreads to other left hemisphere regions (Rogalski et al. 2011b, Rohrer et al. 2013).

Few studies have investigated the anatomic distribution of GM atrophy in patients with autopsy-confirmed disease. In each of the autopsy series described above, a small number of antemortem imaging studies revealed left temporal–parietal GM atrophy (Giannini et al. 2017, Mesulam et al. 2014b). Reports of hippocampal atrophy in lvPPA have also been inconsistent (Gorno-Tempini et al. 2008, Josephs et al. 2013a), despite a statistical association between lvPPA and AD pathology. Some researchers have reported no observable difference in neurofibrillary tangle (NFT) density in hippocampus between lvPPA and clinical AD (Josephs et al. 2013a), consistent with these patients having amnesic AD, whereas others have reported minimal NFT pathology in the hippocampus of patients with lvPPA (Gefen et al. 2012).

Given the high degree of variability in presentation and many potential confounds, and given the goal of identifying a phenotype that reliably reflects a nonamnesic language variant with AD pathology, an essential perspective needed to develop reliable clinical features for lvPPA must come from careful study of autopsy-confirmed samples. In a large cohort of autopsied progressive aphasics in which approximately half had AD pathology (Mesulam et al. 2008, 2014b), lvPPA was the initial syndromic characterization of most patients with AD pathology. Although fluency, single-word comprehension, and grammar were largely preserved at the initial evaluation of these patients, the patients were consistently impaired in their lexical retrieval and often had repetition deficits. Three additional patients had grammatical difficulty at presentation, and one also had comprehension difficulty. Although lvPPA was associated with AD pathology more often than with FTLT-tau or FTLT-TDP pathology, the sensitivity, or ability to use lvPPA to detect a pathologic diagnosis of AD, was only 50%, and the specificity, or ability to exclude other diagnoses, was only 71% compared with a non-AD pathologic diagnosis. When the criteria were modified to include patients

with mixed progressive aphasia (i.e., patients with both comprehension and grammatical difficulty, regardless of the presence of impaired repetition), sensitivity for AD pathology was 56% and specificity was 58%.

In a second large series of well-characterized lvPPA cases (Giannini et al. 2017), investigators also encountered difficulty clearly identifying the subset of PPA cases with AD pathology using published lvPPA criteria. In this study, AD neuropathology was found in 5 (83%) of 6 patients meeting strict published lvPPA criteria at presentation, although this number represented only 26% of the PPA patients with AD pathology in this study. Within the broader logopenic spectrum, including patients with narrowly defined lvPPA, those with lvPPA plus grammatical or lexical comprehension difficulty, and those with lvPPA but less marked repetition difficulty, AD pathology was found in 14 (73%) of 19 patients. Notably, when these patients were followed longitudinally, only 4 developed significant deficits in memory and visuospatial domains, consistent with a clinical diagnosis of typical, amnesic AD. Published lvPPA criteria thus achieved 93% specificity for AD neuropathology, but sensitivity was only 26%. Because word-finding difficulty was ubiquitous among PPA patients regardless of syndromic diagnosis, improvement in identification of clinical features consistent with AD pathology focused on improving the utility of a repetition impairment. Criteria for identifying a clinical repetition deficit in speech have proven quite difficult: Should a repetition deficit include a lexical addition, reordering, or omission? Should a deficit also include a speech sound error, addition, or omission? To circumvent these challenges, investigators evaluated repetition using forward digit span. Using a repetition criterion of four digits forward and omitting the exclusion of individuals with single-word comprehension difficulty or slowed speech, these criteria achieved 94% sensitivity and 67% specificity, with an area under the curve of 0.80.

In a third autopsy study of 52 patients (Harris et al. 2013), pathologic diagnosis was mixed in those with a clinical diagnosis of lvPPA. Only 6 (46%) of 13 lvPPA patients had AD pathology, and 5 of those cases had episodic memory difficulty. Thus, these large studies had considerable difficulty using published lvPPA criteria to identify cases with AD pathology, and found it necessary to modify lvPPA criteria in order to achieve some success in identifying those with AD pathology. From a linguistic perspective, these cases emphasize the heterogeneity of language disorders, and the importance of considering processing deficits—such as impaired auditory–verbal short-term memory—that may not fit within a narrow linguistic consideration of language disorders.

5. BEHAVIORAL VARIANT FRONTOTEMPORAL DEGENERATION

Patients with bvFTD are significantly impaired in their social comportment and personality. These patients can be disinhibited. For example, they may approach strangers on the street to make socially inappropriate comments or reveal private, personal details. They can be hyperoral without being sated and hypersexual, and often act in a childlike manner. They can display explosive agitation without apparent provocation. In contrast to explicitly inappropriate behaviors such as these, they can exhibit apathy, with a limited range of interactive emotion with their partners and children. This apathy may become quite profound, with limited initiation of any behavior even in response to highly motivating

factors. Another class of behaviors observed in bvFTD is obsessions and compulsions. Some of these repetitive behaviors can be quite complex, for instance, developing idiosyncratic political or religious beliefs that penetrate all aspects of their lives, creating elaborate collections of unusual objects, or initiating novel and unusual hobbies such as creating crossword puzzles. Other compulsive behaviors can be simple, repetitive, motor activities, such as clapping, rubbing, whistling, or grinding teeth. There is little perspective-taking, resulting in limited empathy with others, and patients have no insight into the awkward and disturbing nature of their unusual behaviors.

Despite this range of impaired social behavior and personality, patients with bvFTD do not have an obvious aphasia. While these patients' disinhibited behavior can at times lead to speaking in tongues or exaggerated prosodic contours, and while apathy can eventually lead to mutism, their performance on traditional measures of aphasia is often within normal limits. Thus, they have few deficits in measures of visual confrontation naming, and their conversational speech is typically without obvious linguistic impairment. Careful examination of these patients nevertheless reveals that they have subtle but meaningful difficulty with a variety of language measures, including disorders of prosodic expression, difficulty with comprehension and expression of abstract words, impaired comprehension of grammatically complex sentences, and deficits in narrative comprehension and expression. Together, these difficulties interfere with the conversational discourse that is crucial to human interactions, and emphasize a role for the right hemisphere in language.

5.1. Clinical Features

First, consider intonation and prosody in bvFTD. Spouses and caregivers are often struck by the limited range of emotional expression in patients with bvFTD, which may reflect the patients' constrained repertoire of emotional behaviors and their limited ability to use prosody in their emotional expressions. Notably, prosody also plays a role in nonemotional speech, such as the rising pitch at the end of a question requiring a yes or no response. Nevler et al. (2017) conducted an acoustic analysis of a semistructured speech sample in bvFTD. The speech sample was elicited by description of a standard picture known as the cookie theft scene. When describing this picture, bvFTD patients expressed themselves with a limited fundamental frequency range in their speech. This deficit did not correlate with the linguistic characteristics of the speech sample, such as word fluency or grammatical complexity. Moreover, the limited prosodic range did not correlate with an assessment of behaviors in the Neuropsychiatric Inventory, suggesting the possibility of an independent impairment in suprasegmental speech expression that exaggerates the patients' personality and emotional disorder.

Next, consider a limitation in the vocabulary of patients with bvFTD. The single-word semantic memory studies discussed in the context of svPPA, above, provide examples of how the storage of sensory and motor feature knowledge associated with objects may be compromised. What about concepts without direct physical referents in the real world? For example, how would the meaning of abstract concepts like 'hope' or 'truth' be stored in the brain? Much less is known about the neural representation of abstract concepts, even though words referring to abstract concepts tend to be used much more commonly in our daily

speech than words referring to concrete concepts. In a careful analysis of the concreteness of words used to describe the cookie theft scene, patients with bvFTD were found to use significantly fewer abstract words compared with both healthy controls and patients with svPPA (Cousins et al. 2017). In a parallel study, patients with bvFTD also demonstrated a significant concreteness effect in their comprehension on a two-alternative forced-choice associativity judgment task, with significantly worse performance for abstract words than concrete words compared with healthy controls (Cousins et al. 2016).

The reason for this deficit with abstract words is unknown. One hypothesis relates performance to a specific limitation of executive control. Whereas referents of concrete words have physical or temporal existence and thus appear in a relatively consistent and narrow set of contexts, abstract words tend to be more semantically diverse, appear in a larger variety of contexts, and have more variations in meaning. Because of this reliance on context, abstract word meaning may depend in part on executive control governing a semantic search mechanism that regulates meaning selection in a manner that is consistent with the context of the abstract word (Hoffman et al. 2010, Jefferies 2013). This is known as the context availability hypothesis, which posits that abstract word meaning depends in part on the associated context (Schwanenflugel et al. 1988, Schwanenflugel & Stowe 1989). Relevant context facilitates the recognition of abstract words, so that they are processed as quickly as concrete words (Schwanenflugel & Shoben 1983, van Hell & De Groot 1998).

Alternate hypotheses include the so-called dual-coding theory. From this perspective, abstract concepts rely primarily on a system of verbal associations, whereas concrete concepts rely on both visual and verbal associations (Paivio 1991). Because abstract concepts rely on only one of these representational systems, this class of words may be generally more vulnerable to impairment relative to words with concrete referents that can also derive meaning in part from the sensory-motor representations of objects associated with the words. Evidence less consistent with this hypothesis comes from the fact that difficulty with abstract words in bvFTD is doubly dissociated from difficulty with concrete words in svPPA (Cousins et al. 2016, 2017), suggesting that the number of representational systems alone cannot fully explain dissociations between abstract and concrete words.

Several studies also have observed deficits at the level of sentence processing in bvFTD (Ash et al. 2006, Charles et al. 2014). According to detailed analyses of semistructured speech samples, bvFTD patients produce sentences with fewer dependent clauses than healthy controls (Ash et al. 2006). This disparity may be related in part to the executive resource demands associated with sentences that are longer and contain more propositions, that is, sentences that depend in part on greater grammatical complexity. To assess this possibility, investigators studied comprehension in bvFTD using sentences that varied in their grammatical complexity, the number of propositions that they contained, and the length of the gap between grammatically linked elements. To minimize task-related confounds involving decision making and working memory, the investigators used a simple study design that involved visually presented sentences and pictures with a two-alternative forced-choice design, and these materials remained available for patients during consideration of each sentence. bvFTD patients were found to be significantly impaired in their comprehension of lengthy center-embedded sentences containing three propositions (Charles

et al. 2014). By comparison, performance improved when sentences were not center-embedded, contained fewer propositions, or were shorter. This study also found a correlation between comprehension accuracy and performance on measures of executive functioning in bvFTD such as working memory and mental flexibility.

Now, consider a disorder of narrative comprehension and expression in patients with bvFTD. We naturally communicate around the family table and the workplace water fountain with narrative: We bring together acoustic, phonologic, lexical, and grammatical abilities to exchange stories with our family and friends. Narratives are not random strings of thoughts, but instead reflect an organized story with an introductory setting, a sensibly structured set of events, and a summary. Investigators assessed narrative expression in bvFTD by asking patients to describe a wordless children's picture story, "Frog, Where Are You?" (Ash et al. 2006). In addition to phonologic, lexical, and grammatical properties of expression, we assessed the organization of the narrative, including expression of the story's main theme, some recognition of the event organization of the story, and the transitions between these events. We found that the patients with bvFTD showed impaired narrative organization. They exhibited poor appreciation of the organization of the events constituting the story, deficits expressing transitions between elements of the narrative, and impaired appreciation of the overall theme or "punch line" of the story (Ash et al. 2006). By comparison, these patients were very accurate at describing the content of each picture within the story. This study also found that executive deficits in bvFTD patients correlated with their poorly organized narrative expression. A follow-up study showed difficulty with narrative organization during comprehension (Farag et al. 2010). Patients with bvFTD thus had difficulty understanding the organizing relationship between events within familiar narratives, such as 'going fishing' or 'wrapping a gift.' Narrative comprehension performance in bvFTD was associated with executive deficits as well.

Finally, patients with bvFTD are impaired at conversational exchanges. Beyond the many linguistic components contributing to a narrative, conversational exchanges depend in part on perspective-taking to optimize communicative efficacy with a conversational partner. This complex social function involves turn-taking signaled by various pragmatic elements, such as pauses and facial expressions, and more importantly an appreciation of a conversational partner's knowledge and expectations concerning the topic. In one study, patients with bvFTD showed significant difficulty establishing a focal point that could mediate unspoken information exchange based on knowledge that is external to a conversation (McMillan et al. 2012). In this study, patients were asked to give a response to a simple question (e.g., 'Can you give me a boy's name?') that is similar to the answer provided by a similar person to another examiner in the next room. Control subjects increased the probability that their response would match that of a similar person by providing a response that is relatively representative of the domain (in this case, the common male name John). Patients with bvFTD, by comparison, provided random responses that did not take into consideration the stranger's perspective. These patients were also impaired at understanding other pragmatic entailments in discourse (McMillan et al. 2013).

In yet another study (Healey et al. 2015), we asked patients with bvFTD to describe to an avatar the movement of a toy from the floor to a bookshelf. The bookshelf contained other

toys, some of which overlapped with features of the moved object. Healthy controls modified the adjectives used to describe the moved object in order to distinguish the moved object from a competitor on the shelf. For example, when a small, green frog was on the floor and a large frog and a pink frog were on the shelf, it would not be appropriate to simply state ‘the frog is on the shelf.’ Instead, controls stated ‘the green frog. . .’ or ‘the small frog. . .’ when describing the location of the moved object. By contrast, the patients with bvFTD did not modify or even use an adjective to clearly designate the moved object, demonstrating their insensitivity to the perspective of a conversational partner (Healey et al. 2015). In another condition, patients with bvFTD were asked to describe this scene to a color-blind conversational partner. Despite aural and printed reminders that the partner was color-blind, these patients did not avoid using a color adjective, thus differing from healthy controls (Healey et al. 2015).

5.2. Anatomic Features

Patients with bvFTD are typically found to have GM atrophy in the frontal lobe (including medial, dorsolateral, and orbital areas) and the temporal lobe, particularly in the right hemisphere. Regression analyses have associated poor bvFTD performance on the linguistic measures described above with this anatomic substrate. The limited range of prosodic expression found in bvFTD (Nevler et al. 2017) was associated with GM atrophy of the insula and orbital regions of the right frontal lobe, areas frequently diseased in these patients. Anatomic findings in bvFTD associated poor abstract word knowledge with GM atrophy in the inferior frontal gyrus and insula bilaterally (Cousins et al. 2016, 2017). The inferior frontal gyrus, a region otherwise thought to be important for semantic control (Moss et al. 2005, Thompson-Schill 2003, Thompson-Schill et al. 1997), is thought to play a role in meaning selection and the integration of contextual information when processing abstract words (Hoffman et al. 2010, 2015; Wang et al. 2010). This hypothesis is consistent with findings from recent meta-analyses identifying the most common loci of activation in fMRI and PET studies of abstract versus concrete conceptual representations in healthy adults. This research found that abstract concepts elicit greater activity in the left inferior frontal gyrus, left anterior middle temporal gyrus, and left anterior superior temporal gyrus. By comparison, concrete concepts elicited greater activity in bilateral angular gyrus, left posterior cingulate, precuneus, left fusiform gyrus, and left parahippocampal gyrus (Binder et al. 2005, 2009; Wang et al. 2010), and many of these regions are associated with the visual processing system and are compromised in patients with svPPA who have difficulty with object knowledge.

bvFTD patients’ difficulty understanding grammatically complex sentences was related to extensive GM atrophy in several frontal and temporal regions (Charles et al. 2014). Because most of the regressions were in the right hemisphere, we suspect that this comprehension deficit in bvFTD was not primarily linguistic in nature but rather related to the resource limitations that contributed to their comprehension deficits. Consistent with this view, many of the same GM regions implicated in the patients’ grammatical comprehension deficit were also associated with their difficulty understanding lengthy sentences. Among these were prefrontal areas important for strategic organization, the anterior cingulate region important for attention and initiation, and posterior–superior temporal and inferior parietal regions

implicated in short-term memory. Consistent with the bilateral nature of the brain regions contributing here to grammatical comprehension difficulty, extensive correlations also related comprehension performance to WM areas, including corpus callosum and corona radiata. These WM areas contain projections mediating connections between brain areas supporting resource-related functions and the core language network in the left perisylvian region. Moreover, WM regions implicated in both grammatical and resource-related aspects of sentence comprehension were quite similar. Regression analyses have also related right frontal and temporal GM atrophy to impairments in sentence expression, suggesting a common source of anatomic deficit across both comprehension and expression of sentences in bvFTD.

Narrative comprehension difficulty in bvFTD has been associated with bilateral anterior and medial frontal GM atrophy, more pronounced in the right hemisphere than the left hemisphere (Farag et al. 2010). This area of right hemisphere atrophy overlapped with healthy control subjects' pattern of recruitment in an fMRI study using the same materials. Regression analyses similarly showed that difficulty with narrative expression is associated in part with right dorsolateral pre-frontal and right anterior temporal GM atrophy (Ash et al. 2006). Performance on tasks requiring comprehension of discourse was related to GM atrophy in right frontal regions, including ventral and dorsolateral prefrontal areas (Healey et al. 2015, McMillan et al. 2013).

6. SUMMARY

Progressive aphasia results in relatively discrete disorders of language. svPPA interferes with word meaning, particularly words representing object concepts, and naPPA compromises the ability to understand and express words composing a sentence. IvPPA is associated with auditory–verbal short-term memory difficulty, a crucial component of language processing. bvFTD interferes with organizing sentences into larger narrative units, and exchanging these effectively in the course of a conversation.

Each of these components of a language system is associated with disease affecting a relatively discrete cerebral network. Disease in svPPA is thus centered in the left anterior temporal lobe, and disruption of the semantic memory system by GM and WM disease in this area is consistent with the hypothesis that the semantic memory system is a biologically validated component of language. By comparison, disease in naPPA is centered primarily in the left inferior frontal lobe, and impairment of the grammatical system by disease in a network centered in this GM and WM area supports the hypothesis that grammatical processing is a biologically validated aspect of language. The crucial role of auditory–verbal short-term memory in language processing is underlined by the significant impact of this deficit following disease centered in the left lateral temporal–parietal region. Finally, narrative and conversational exchanges are significantly impaired by disease in a network centered in the frontal lobe, and focal disease causing an interruption of pragmatic aspects of communication is consistent with the claim that narrative discourse is a biologically validated aspect of language. These semantic, grammatical, short-term memory, and pragmatic aspects of communication are thus essential aspects of language, and their

association with specific cerebral networks underlines their importance for a theory of language.

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