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Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration

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Abstract

Frontotemporal lobar degeneration (FTLD) can manifest as a spectrum of clinical syndromes, ranging from behavioural impairment to language or motor dysfunction. Recently, revised diagnostic criteria have been proposed for the behavioural and progressive aphasia syndromes associated with frontotemporal degeneration. The present review will summarize these diagnostic guidelines and highlight some lingering controversies in the classification of FTLD clinical syndromes. We will discuss common tools and methods used to identify the insidious changes of behavioural variant frontotemporal dementia (bvFTD), the value of new, patient-based tasks of orbitofrontal function, and the issue of a benign or ‘phenocopy’ variant of bvFTD. With regard to primary progressive aphasia (PPA), we will discuss the scope of the semantic disorder in semantic-variant PPA, the nature of the speech disorder in non-fluent, agrammatic PPA, and the preliminary utility of a logopenic PPA classification.

Introduction

Frontotemporal lobar degeneration (FTLD) is a common cause of pre-senile dementia, accounting for 5–17% of autopsy-proven cases presenting under the age of 70 (Barker et al., 2002; Knopman et al., 1990). It can manifest as a spectrum of clinical syndromes, ranging from behavioural impairment to language or motor dysfunction. Recently, revised diagnostic criteria have been proposed for the behavioural variant of frontotemporal dementia (bvFTD) (Rascovsky et al., 2011) and FTLD- associated aphasic syndromes, now subsumed under the rubric of primary progressive aphasia (PPA) (Gorno-Tempini et al., 2011). The present review will summarize these revised diagnostic guidelines, as well as lingering controversies in the clinical diagnosis of FTLD.

Controversies in the diagnosis of behavioural variant FTD

Diagnosis of bvFTD

The behavioural variant of frontotemporal dementia (bvFTD) is a clinical syndrome characterized by progressive changes in personality, social comportment, and cognition. These behavioural and cognitive changes are due to degeneration of frontal and anterior temporal regions associated with a heterogeneous set of pathologies (Mackenzie et al., 2009, 2010). Despite recent advances in the characterization of bvFTD, diagnosis of the syndrome remains challenging. Many bvFTD patients are ostracized by family and friends, lose their jobs, and endure multiple referrals before their disease is recognized as a neurodegenerative

disorder. Even when patients are identified as suffering from a neurological problem, they are often misdiagnosed with Alzheimer's disease or other forms of dementia (Mendez et al., 1993, 2007; Varma et al., 1999). Early and accurate diagnosis of bvFTD is crucial, as it allows for appropriate therapeutic and behavioural management of patients, as well as adequate counselling of families and caregivers.

In the absence of definitive biomarkers, diagnosis of bvFTD should be made on the basis of valid clinical criteria coupled with diagnostic methods that are practical and easily available. Four sets of diagnostic criteria have been published since 1994 (Brun et al., 1994; McKhann et al., 2001; Neary et al., 1998; Rascovsky et al., 2011) and reflect our evolving understanding of the disorder. Based on this accumulated experience, the International bvFTD Criteria Consortium (FTDC) developed revised guidelines for the diagnosis of bvFTD (Rascovsky et al., 2011). In contrast to previously established guidelines (Neary et al., 1998), the FTDC criteria are structured as a hierarchy based on levels of diagnostic certainty (see Table 1). Possible bvFTD is a purely clinical diagnosis, requiring the presence of three of six behavioural and cognitive features: disinhibition, apathy/inertia, loss of empathy, perseverative/compulsive behaviours, hyperorality and a dysexecutive neuropsychological profile. This flexible classification allows for variable symptom profiles at onset and aims to identify patients at the mildest stages of disease. A diagnosis of probable bvFTD attempts to classify patients with a high probability of underlying FTLN pathology, and is based on the clinical syndrome plus demonstrable functional decline and frontotemporal imaging changes. Finally, classification of bvFTD with definite FTLN pathology is limited to patients with the clinical syndrome and evidence of a pathogenic mutation or FTLN histopathology. In a large, multisite study, the FTDC criteria were significantly more sensitive than previously established criteria in a cohort of bvFTD patients with known FTLN pathology (86% versus 53%). (Rascovsky et al., 2011). Although increased sensitivity may translate into early detection of the bvFTD syndrome, further studies are needed to establish the reliability and specificity of these revised diagnostic guidelines.

How should behaviour be measured? Objective versus subjective methods

While most researchers agree on the core behavioural features that constitute the bvFTD syndrome, there are lingering questions regarding the tools and methods required to identify these behavioural changes. Detecting and measuring behavioural alterations in bvFTD is difficult for several reasons. First, while psychiatric symptoms such as delusions and hallucinations are easily identified and classified as pathological, rating of features such as 'disinhibition' is highly subjective and depends on culture and situational context (Ibanez & Manes, 2012). For example, expletives or sexually explicit jokes may be acceptable amongst close friends, but considered inappropriate at work or religious settings. In a similar manner, flirting or complimenting the opposite sex may be frowned upon in some cultures, but virtually expected in others. Second, the insidious and often subtle nature of these behavioural changes, coupled with the challenges and stressors of midlife, can lead to psychiatric diagnoses such as depression, bipolar disorder or even late-life schizophrenia (Manes, 2012; Woolley et al., 2011). A bvFTD diagnosis is further confounded if the patient has a long-standing history of 'eccentric' behaviour or the primary informant has limited contact with the patient (e.g. grown children living in separate households).

Taking these caveats in mind, how can we measure the personality and behavioural changes characteristic of bvFTD? We can generally divide these approaches into objective and subjective methods. Subjective self-report scales are commonly used to measure internal states, attitudes, beliefs or personal preferences. However, they crucially depend on patient introspection and language comprehension. Given the lack of insight typical of bvFTD patients, these scales can be misleading and should not be relied upon for diagnosis.

Caregiver surveys circumvent issues of insight and comprehension and have the added advantage of providing information about the patient in context (e.g. at home, in social events) and over prolonged periods of time. For quantification of these behaviours, many researchers rely on behavioural scales such as the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994), the Cambridge Behavioural Inventory (Bozeat et al., 2000a; Wedderburn et al., 2008), or the Frontal Behavioural Inventory (FBI) (Kertesz et al., 2000). Although caregiver questionnaires represent an improvement over self-report measures, caregiver rating of behavioural features is still inherently subjective. Furthermore, the severity of symptoms may be coloured by the overall health, stress and personality of the caregiver (Mioshi et al., 2009a). Caregiver surveys that require inference of the patient's mood or cognition add yet another level of complexity. For example, a modified caregiver version of the Interpersonal Reactivity Index (a commonly used measure of empathy) includes questions such as 'The subject tries to look at everybody's side of a disagreement before he/she makes a decision' (Davis, 1983). These inferences may be difficult, if not impossible for caregivers to determine. Given these concerns, rating of aberrant comportment should, whenever possible, be based on overt behaviours as opposed to inferences about a patient's cognitive or emotional state.

Objective methods for rating behaviour include clinical observation and objective testing. In order to make reliable behavioural observations, clinicians need a considerable level of expertise in the identification and rating of abnormal behaviour. There are very few scales to guide clinicians in this endeavour. Notably, Rankin and colleagues developed the Social Observer Behavior Checklist, which quantifies spontaneous social behaviour during regular cognitive evaluations (Rankin et al., 2008). The checklist allows the clinician or psychometrician to rate observable signs of inertia, perseveration, disregard for social norms, etc. Although extremely useful as an objective clinical measure, the information acquired by this checklist is inevitably limited by time and context. Patients will rarely exhibit florid disinhibited or aggressive behaviours in a 1-h clinical evaluation. Furthermore, the checklist cannot evaluate behaviours that occur at home such as rituals, collecting/hoarding or appetite and sleep changes. The clinical context may also mitigate spontaneous aberrant behaviours by introducing a significant amount of external structure, in a way acting as the patient's 'frontal lobes' (Ibanez & Manes, 2012). Given the shortcomings of subjective measures and clinical observation, the challenge in the next couple of years will be to devise objective, patient-based tests capable of quantifying characteristic bvFTD behaviours. Novel patient-based approaches are already underway to test apathy/inertia (Massimo et al., 2012) and environmental dependency in clinical settings (Ghosh & Dutt, 2010). This exciting prospect will require a multidisciplinary approach at the intersection of neuropsychology, psychiatry and neuroscience, and will complement valid caregiver scales that quantify behaviours in context and over long periods of time.

Should social cognition and decision-making tasks replace traditional executive measures in the diagnosis of bvFTD?

While behavioural changes tend to dominate the initial presentation of bvFTD, cognitive deficits appear as the disease progresses (Mendez et al., 2007). When this cognitive profile emerges it is usually characterized by executive and generation deficits in the context of relatively preserved memory and visuospatial functions (Diehl et al., 2005; Elfgrén et al., 1994; Grossman et al., 2007; Kramer et al., 2003; Lindau et al., 1998; Mendez et al., 2009; Pachana et al., 1996; Perry & Hodges, 2000; Rascovsky et al., 2002, 2008; Walker et al., 2005). Although the overall pattern of cognitive impairment appears to be useful in differential diagnosis, single studies of specific cognitive abilities have yielded inconsistent results. In particular, the value of traditional 'frontal' or 'executive' measures in the differential diagnosis of bvFTD has been called into question. For example, while some

studies have demonstrated greater fluency, abstraction and cognitive flexibility deficits in bvFTD compared to AD (Diehl et al., 2005; Frisoni et al., 1995; Heidler-Gary et al., 2007; Hornberger et al., 2010; Kertesz et al., 2003; Lindau et al., 1998; Perri et al., 2005; Rascovsky et al., 2007, 2008; Thomas-Anterion et al., 2000), others have failed to find differences on traditional executive tasks such as the Stroop test, the Wisconsin Card Sorting Test (WCST) and the Raven's Progressive Matrices (Frisoni et al., 1995; Heidler-Gary et al., 2007; Libon et al., 2007a; Nedjam et al., 2004; Pachana et al., 1996; Rosen et al., 2004a; Thomas-Anterion et al., 2000). As with any cognitive construct, a combination of executive measures may prove more useful for differential diagnosis than a comparison of individual test performance. For example, Torralva and colleagues (Torralva et al., 2009a) found adequate discrimination of bvFTD and AD patients using the INECO Frontal Screening (IFS), while a study by Hornberger and colleagues (Hornberger et al., 2010) showed that 89% of bvFTD and AD patients were correctly classified based on their performance on letter fluency, digit span backward and the Hayling test of response inhibition.

Given that bvFTD is primarily a disease of the frontal lobes, the inconsistent value of frontal/executive tests in differential diagnosis is puzzling. There are at least three theoretical explanations for these confusing results (Johns et al., 2009; Millar et al., 2006). First, the sensitivity of traditional executive tasks may be minimized by the inherent structure of a cognitive evaluation. For this reason, some researchers argue for the use of ecologically valid planning and organizing tasks which are thought to reflect everyday dysexecutive errors. Measures such as the Multiple Errands Task and Hotel Task appear to be impaired early in bvFTD compared to controls (Gleichgerricht et al., 2010b; Torralva et al., 2009b), but their role in the differential diagnosis of dementia remains unknown. Second, impairments in executive skills, while present in bvFTD, are not specific to this condition (Kumar et al., 1990). Executive deficits can be present in mild AD and are common in syndromes with prominent fronto-subcortical dysfunction such as progressive supranuclear palsy (PSP) and dementia with Lewy bodies. Finally, and perhaps most importantly, some traditional 'executive' tasks measure dorsolateral integrity rather than orbitofrontal/ventromedial functioning (the latter believed to be more severely compromised early in the course of bvFTD (Seeley et al., 2008)). Given the failure of traditional neuropsychological tests to capture early changes in bvFTD, new tools have been proposed to assess functions attributed to orbital and ventromedial integrity, such as emotion, social cognition and decision-making.

Emotional reactivity and recognition

Although bvFTD patients show adequate emotional reactivity when confronted with stimuli that elicit simple emotions (e.g. emotion-eliciting films, acoustic startle (Sturm et al., 2006; Werner et al., 2007)), some studies point to disproportionate impairments in the recognition of negative emotions such as anger, fear and disgust (Keane et al., 2002; Kipps et al., 2009a; Lavenu & Pasquier, 2005; Lough et al., 2006; Werner et al., 2007). These recognition deficits have been associated with damage to a large, right-predominant network involving orbitofrontal cortex, insula, amygdala, and lateral and inferior aspects of the temporal lobe (Kipps et al., 2009b; Rosen et al., 2004b; Werner et al., 2007). Interestingly, even mild bvFTD patients show prominent alterations in the experience and expression of self-conscious emotions, such as amusement and embarrassment (Sturm et al., 2006, 2008). Difficulties processing negative and self-conscious emotions may underlie deficits in the recognition of sarcasm and other forms of social censure (Kipps et al., 2009b) and contribute to the loss of empathy typical of bvFTD. While these tests hold promise for use in differential diagnosis, their specificity with regard to bvFTD remains unknown. Studies using static emotional stimuli have found emotion recognition deficits in Huntington's disease (HD) (Henley et al., 2012) while a study using dynamically changing emotions

found comparable emotional tracking impairments in diverse neurodegenerative syndromes (bvFTD, PPA, CBS, PSP and AD) (Goodkind et al., 2011). Clearly, future research is needed to elucidate the utility of emotion reactivity and recognition tasks in the diagnosis of bvFTD.

Theory of mind

The social impairments of bvFTD patients may also be partially explained by their reported deficits in mentalizing or theory of mind (ToM) (for a review see Adenzato et al., 2010). ToM is defined as the ability to assess the desires, beliefs and intentions of other people and is thought to be critically subserved by rostral aspects of the medial prefrontal cortex (Amodio & Frith, 2006). While bvFTD patients exhibit variable deficits in first- and second-order false belief tasks (e.g. X believes Y, or X believes that Z believes Y), they often fail tests of emotional attribution, such as the faux pas, judgement of preference, and Reading the Mind in the Eyes (RME) tests (Gregory et al., 2002; Snowden et al., 2003; Torralva et al., 2009b). Of note, most ToM tests use stories, cartoons or vignettes that require complex processing and multiple cognitive abilities. At least two studies have found a relationship between ToM performance and executive dysfunction, making it difficult to ascribe failure in complex ToM tasks to a selective deficit in mentalizing or perspective-taking (Eslinger et al., 2007; Snowden et al., 2003). This view is further supported by studies that show frank ToM impairments in mild patients with various neurodegenerative syndromes including AD, PD and HD (Bodden et al., 2010; Freedman et al., 2012; Freedman & Stuss, 2011; Roca et al., 2010).

Moral knowledge and judgement

Despite reports of sociopathic acts in bvFTD (Mendez et al., 2005b), bvFTD patients appear to have preserved knowledge of moral rules and conventional norms (Lough et al., 2006; Mendez & Shapira, 2009; Mendez et al., 2005a). However, they are likely to provide 'utilitarian' responses when confronted with hypothetical moral dilemmas (Mendez & Shapira, 2009). For example, in the 'footbridge dilemma', bvFTD patients are more likely than AD patients and controls to push an innocent man off a footbridge (thus murdering him), in order to save the life of five people who would otherwise be killed by an approaching train (Gleichgerricht et al., 2011; Mendez & Shapira, 2009). This abnormal utilitarian response has been linked to impairments in affective ToM tasks (Gleichgerricht et al., 2011) and right frontotemporal dysfunction (Mendez & Shapira, 2009). While certainly intriguing, the specificity of these tasks in the differential diagnosis of bvFTD still needs to be ascertained.

Decision-making tasks

Decision-making in bvFTD can be formally studied using experimental tasks that vary risk, reward and punishment (see Gleichgerricht et al., 2010a for review). Several studies have used the Iowa Gambling Task (IGT) (Bechara et al., 1994) to study decision-making in bvFTD. In this task subjects are asked to pick cards from decks that yield a particular pattern of rewards. As the game proceeds, normal subjects adopt a conservative strategy of accepting smaller wins in order to avoid large losses, while mild bvFTD patients consistently choose cards from decks that offer large wins and even greater losses (Torralva et al., 2009b). Although bvFTD patients exhibit clear impairments in the IGT, the critical cognitive substrate for this deficit remains controversial. The IGT is a complex task requiring multiple executive abilities (e.g. working memory and reversal learning) which also depend on dorsolateral integrity (Fellows & Farah, 2005). Not surprisingly, studies have shown altered IGT performance in several neurological and psychiatric conditions including AD (Sinz et al., 2008), PD (Delazer et al., 2009) and schizophrenia (Sevy et al., 2007).

The role of context in the decision-making of bvFTD patients has also been studied using real-world scenarios (Grossman et al., 2010). bvFTD patients were asked to judge the relative acceptability of scenarios that were embellished with a positive, socially rewarding context (e.g. going through a red light when rushing a sick child to an ER) or a negative, socially penalizing context (e.g. going through red light when there is a police car at the intersection). Compared to AD patients and controls, bvFTD patients appropriately shifted their acceptability judgements of positively valenced scenarios but were insensitive to the socially penalizing value of negative scenarios. Clearly, 'decision-making' is a complex construct that depends on multiple cognitive abilities and brain regions (Gleichgerrcht et al., 2010a). Further research is needed before we can include these multi-dimensional tasks in formal diagnostic algorithms for bvFTD.

Use of experimental tasks in everyday clinics

The study of emotion, social cognition and decision-making is of great theoretical interest in bvFTD research, and may provide important insights into the role of ventromedial and orbitofrontal brain regions. Compared to traditional executive tasks, these experimental tasks assess functions that are more representative of the everyday symptoms and difficulties of bvFTD patients. However, several issues need to be resolved before these novel approaches are implemented as a standard in clinical diagnosis. First, although designed to selectively test ventromedial/orbitofrontal integrity, most of these tasks are complex and demand executive resources dependent on dorsolateral prefrontal regions. Second, these anatomical concerns raise questions regarding the sensitivity and specificity of experimental tasks in differential diagnosis. Finally, the use of experimental tasks in routine clinical practice must balance theoretical versus practical concerns. Most of these tasks are time-consuming and require specialized stimuli and training. In order to be diagnostically useful, researchers will need to develop short and simple task adaptations that are suitable for use in general clinical settings (Sarazin et al., 2012). The diagnostic value of these novel approaches will ultimately depend on their ability to discriminate over and above the often robust cognitive profiles obtained by traditional neuropsychological measures.

What are phenocopies?

Studies of function and disease progression in bvFTD have uncovered a benign form or 'phenocopy' of the disorder. Although phenocopy patients may have identical behavioural features compared to those with 'true' bvFTD, functional abilities are generally preserved and imaging abnormalities are absent (Davies et al., 2006; Kipps et al., 2007, 2009c; Mioshi et al., 2009b; Piguet et al., 2009). Importantly, patients with a 'phenocopy' syndrome do not decline cognitively or socially (Hornberger et al., 2009; Piguet et al., 2011). The aetiology of 'phenocopy' cases remains unknown, but some authors speculate that phenocopy cases may reflect psychiatric or autism-Asperger's spectrum patients that decompensate in mid-life (Kipps et al., 2010; Manes, 2012; Piguet et al., 2011). An intriguing hypothesis has recently surfaced regarding the underlying pathology of a subset of phenocopy cases. Recently, Khan and colleagues reported two bvFTD cases with a relatively stable clinical course (2 and 7 years) that were later found to have a C9 mutation (Khan et al., 2012). This finding may have implications for the diagnosis of ambiguous bvFTD cases with very subtle atrophy and slow disease progression.

Controversies in the diagnosis of primary progressive aphasia

Clinical recommendations for diagnostic criteria of primary progressive aphasia (PPA) have been published recently (Gorno-Tempini et al., 2011). The criteria are summarized in Table 2. These observations, based on a consensus of international experts, identified clinical diagnostic criteria for each of three variants of PPA. These have generally achieved

recognition throughout the community of active researchers because they provide a common starting point for work performed in different labs that are located in different countries throughout the world.

While the principle of shared criteria is crucially important, this does not necessarily mean that all the investigators agree on the details specified in the criteria. Here we provide some examples of persistent controversies in the diagnostic criteria for PPA. In particular, we describe one controversy associated with each variant of PPA. We underline here the importance of on-going collaborative research that will ultimately lead to an optimized set of criteria for PPA.

Non-fluent/agrammatic primary progressive aphasia: apraxia of speech?

The central characteristic of the non-fluent/agrammatic variant of primary progressive aphasia (naPPA), also known as progressive non-fluent aphasia (PNFA), is effortful, non-fluent speech. Several studies have documented this quantitatively, showing that speech rate in a semi-structured speech sample is less than one third the rate of healthy seniors (Ash et al., 2009; Gunawardena et al., 2010; Rogalski et al., 2011a; Wilson et al., 2010a). At least two hypotheses have been forwarded to explain this essential feature of naPPA. One prominent proposal concerns an impairment of grammatical processing, and the second is concerned with a disruption of the motor speech apparatus. While each of these deficits may slow speech, there appears to be more substantial evidence supporting the former relative to the latter.

Consider first the grammatical processing deficit observed in naPPA. Grammar is essential to the organization of a sentence. Long-distance syntactic relations specify who is doing what to whom among a sentence's constituents, and allow us to specify these crucial relations independent of the superficial characteristics of our speech. Thus, in a pair of sentences like 'It is cats that chase dogs' and 'It is dogs that cats chase,' cats are chasing dogs regardless of word order. This creative flexibility is a uniquely human characteristic that is a universal property of all languages. Without this essential component of sentence processing, the rapid construction of sentences from multiple words is substantially slowed.

There is rigorous evidence consistent with the claim that patients with naPPA have slowed, effortful speech related at least in part to a grammatical deficit. The first kind of evidence comes from a careful analysis of errors in semi-structured speech samples (Ash et al., 2009; Gunawardena et al., 2010; Wilson et al., 2012). This work has demonstrated the reduced frequency of grammatically complex utterances in patients' speech. There is also an increased frequency of frank grammatical errors in naPPA speech. Moreover, these indices of grammatical simplification are significantly correlated with the rate of slowed speech in naPPA.

While slowed speech can be explained in part by a motor speech deficit, there is also a deficit in grammatical comprehension in naPPA that cannot be easily explained by a motor disorder. For example, these patients are impaired at answering a simple question about a sentence that depends on grammatical processing (Grossman et al., 1996; Peelle et al., 2008), have deficits pointing to one of two pictures on the basis of a grammatically complex sentence (Wilson et al., 2010b), and have difficulty ordering words on an anagram task to describe a scene using a grammatically complex question (Weintraub et al., 2009). naPPA patients also have difficulty on executive measures of working memory (Libon et al., 2007b; Libon et al., 2009), but these comprehension studies show impairments independent of the working memory demands of the sentence materials. To prove that deficits in grammatical comprehension are independent of working memory or task-related resource demands, online measures of sentence processing have demonstrated deficits related to grammatical

processing (Peelle et al., 2007; Price & Grossman, 2005). Moreover, these comprehension deficits are correlated with slowed, effortful speech.

The third kind of evidence comes from neuroanatomic studies of speech fluency and grammatical processing deficits in naPPA. Thus, regression analyses relate slowed speech to grey matter atrophy in inferior frontal and anterior-superior temporal regions of the left hemisphere (Ash et al., 2009; Gunawardena et al., 2010; Rogalski et al., 2011a). Likewise, assessments of grammatical processing in comprehension and production also relate these characteristics to left inferior frontal and anterior-superior temporal regions (Gunawardena et al., 2010; Peelle et al., 2008; Rogalski et al., 2011a; Wilson et al., 2010b, 2012).

The second hypothesis is concerned with a disorder of the motor speech apparatus, also known as apraxia of speech (AoS). From this perspective, the rapid coordination of the 31 muscle groups needed for articulation is compromised, thereby slowing speech.

What evidence is available to support this characteristic of naPPA? Perhaps the evidence cited most frequently is the common observation of speech errors in naPPA. There is no doubt that speech errors occur quite commonly in naPPA (Ash et al., 2010; Josephs et al., 2006; Rohrer et al., 2010). There is little evidence, however, that the frequency of speech errors correlates with slowed speech in naPPA. The theory of AoS is difficult to test, moreover, because an operational definition of AoS has proven so elusive. We reasoned that a disorder of the motor speech apparatus should result in the production of a specific kind of speech error. Poorly coordinated muscle groups ordinarily needed for articulatory agility thus should yield speech errors that are distortions of speech sounds not found in the speaker's native language. This is in contrast to speech errors that we all produce and that are governed by the linguistic system of phonology – these errors are substitutions and exchanges of speech sounds that are found in a native speaker's language. The one study examining speech errors in this manner found that speech errors consistent with AoS account for only 21% of the speech errors in naPPA (Ash et al., 2010).

Many patients with AoS have a co-occurring movement disorder, such as progressive supranuclear palsy or corticobasal syndrome (Josephs & Duffy, 2008). It is thus possible that some AoS speech errors are related to the movement disorder per se. Of course this does not challenge the presence of AoS, but does call to question the meaningfulness of AoS as a criterion for naPPA independent of a movement disorder. Our observation is that there are occasional individuals with profoundly distorted speech that cannot otherwise be explained by a co-occurring movement disorder, and a recent report confirms this observation (Josephs et al., 2012). Neuroanatomic studies do not appear to relate phonetic speech errors to a brain region that is discrete enough to be interpretable. Our unpublished work relates phonological speech errors in naPPA to atrophy of the left frontal operculum and anterior insula, an area that is encompassed by the regressions relating slowed speech to the left inferior frontal region. While this observation, if substantiated by additional work, does suggest that the presence of speech errors may serve as a characteristic for naPPA, this is not consistent with the motor-based hypothesized basis for AoS. In sum, there appears to be good evidence for the grammatical characteristics associated with naPPA, but evidence supporting the utility of AoS as a clinical criterion for naPPA appears to require additional work.

Semantic variant primary progressive aphasia: what isn't understood?

The clinical characteristics of the semantic variant of PPA (svPPA), also known as semantic dementia, appear to turn on a disorder of word meaning. This is also thought to be the basis for the profound naming deficit found in these patients. While impairments in naming and word meaning have been described in detail over the past 20 years (Hodges & Patterson, 2007), the basis for this deficit is less clear. One approach argues that the anterior temporal

lobe serves as a 'hub' that integrates modality-specific information represented throughout the cerebrum, and that disease centred in this area compromises the hub that is the basis for semantic memory (Patterson et al., 2007). Another approach, also based on a neuroanatomic model, argues that anterior and ventral portions of the temporal lobe are visual association cortex, and that patients with svPPA are disproportionately compromised in their visual object knowledge compared to other domains (Bonner et al., 2009). Here we examine this controversy.

The semantic deficit in patients with svPPA is well documented. Visual confrontation naming of objects is profoundly impaired, and many studies associate this with poor comprehension of the words that cannot be named (Lambon Ralph et al., 2001; Rogers et al., 2004). On measures of associativity judgement, svPPA patients have difficulty identifying the most meaningful relationship between a target word and two available choices. Much work has been devoted to emphasizing that impairments like this are related to the meaning of the words and the representation of the underlying concept rather than difficulty accessing semantic memory from a lexical representation. An influential study of naming that tracked patients' performance longitudinally showed that naming errors increasingly consist of substitutions that named prototypes (e.g. 'dog' in response to a picture of a camel) or superordinates (e.g. 'animal' in response to a picture of a camel) (Hauk et al., 2007; Lambon Ralph et al., 2001; Patterson, 2007). With visual depictions of objects, patients with svPPA were allowed to view pictures of objects, and then asked to draw the objects as soon as the visual stimulus was removed. The investigators showed that the reproduced objects incorporated many incorrect features of prototypes of the same category. For example, when drawing a picture of a goose from immediate memory, the animal was reproduced with four mammalian-like legs; when asked to draw a frog, the reproduced animal had a tail. Likewise, in their judgements of the coherence of pictures depicting objects, miscoloured pictures were incorrectly accepted as correct when the colour was taken from another member of the same superordinate category, while objects miscoloured with a colour that is not a member of the category were correctly rejected (Ikeda et al., 2006). Finally, there is considerable evidence to suggest that patients with svPPA are also impaired in non-verbal aspects of objects such as their use and their auditory attributes (Bozeat et al., 2000b, 2002; Goll et al., 2009).

These findings have been concerned overwhelmingly with representations of object concepts. Objects strongly depend on visual representations. Since disease in svPPA is centred in ventral and inferolateral portions of the temporal lobe, and since this area is visual association cortex, an alternative account for these observations is that visual feature knowledge essential to the representation of object concepts is degraded in svPPA. This would help explain reported difficulty with other modalities, such as difficulty recognizing the auditory features of an object, since it is the auditory features of visual objects that are being assessed. Later in the disease process, auditory association cortex in more dorsal regions of the temporal lobe may become compromised (Avants et al., 2007; Brambati et al., 2009), and this can add to the longitudinal appearance of a universal semantic deficit. White matter tracts containing reciprocal projections between visual association cortex in the ventral temporal lobe and other modality-specific association regions are compromised in svPPA, and this too can undercut performance on measures of semantic memory in svPPA (Agosta et al., 2010; Duda et al., 2008). Finally, detailed studies examining brain-behavioural relationships in svPPA show regression analyses relating impaired performance on measures of word and object associativity to the fusiform gyrus, an area of the ventral temporal lobe that is part of the visual association cortex (Mion et al., 2010).

One alternative account is that disease in svPPA degrades the representation of visual feature knowledge associated with object concepts. Since visual knowledge plays such a

crucial role in the representation of object concepts, this would explain in part the extensive semantic deficit seen in svPPA. What is the evidence in support of this alternative account? Perhaps the strongest evidence comes from demonstrations of 'reversal of the concreteness effect'. The 'concreteness effect' describes the universal finding that concrete objects have a stronger mental representation than abstract concepts (Paivio, 1978, 1991). The concreteness effect is found on a wide variety of tasks involving word recognition, word reading, and word naming. It is distinctly unusual to find evidence demonstrating that abstract concepts are easier than concrete concepts, yet reversal of the concreteness effect is relatively common in patients with svPPA (Bonner et al., 2009; Breedin et al., 1995; Macoir, 2009; Papagno et al., 2009; Yi et al., 2007). This has been described in several detailed case reports, and more recently in several case series. Moreover, a regression analysis showed that the difference between performance with abstract and concrete stimuli in svPPA is related to disease in the ventral and anterior temporal lobes (Bonner et al., 2009).

What additional evidence is there to support the claim that the semantic memory impairment in svPPA is not universal? This evidence comes from observations that patients with svPPA perform relatively accurately in semantic domains that do not involve object concepts. Two such domains have been examined. One is the domain of numerosity. Numbers define a quantity independent of the nature of the object being counted. 'Fiveness' is a concept that is conserved regardless of whether this quantity is being applied to birds or balls or beliefs. Thus, it is reasonable to consider that concepts of quantity such as number are quite different in their mental representation from object concepts. We have found repeatedly that numerosity and operations involving numerosity such as calculations are relatively preserved in svPPA, and that number knowledge in patients with disease in the parietal lobe is doubly dissociated from object knowledge in patients with svPPA (Cappelletti et al., 2011; Diesfeldt, 1993; Halpern et al., 2004). Rare exceptions show number deficits in occasional svPPA patients who are profoundly impaired (Julien et al., 2008), although our unpublished observations show preserved multi-digit written calculations in profoundly impaired svPPA patients who have minimal comprehension of object concepts and absolutely no confrontation naming ability.

A second domain of relatively preserved knowledge in svPPA appears to be music meaning. While patients with svPPA may have difficulty naming and recognizing musical instruments, they nevertheless are able to appreciate the music played by these instruments (Goll et al., 2009; Hailstone et al., 2009). In a detailed study examining musical knowledge in a patient with profound deficits in word meaning and object naming due to svPPA, the patient was able to sight-read lengthy musical pieces with only 1% errors (Weinstein et al., 2011). When embellishing sparsely notated baroque musical pieces, he did so in a coherent manner consistent with the notated music. Finally, his embellishments were creative and original. While relatively preserved performance with numbers and music does not diminish the profound deficits in naming and object knowledge in svPPA, findings such as these suggest that patients with svPPA do not have a universal deficit in semantic memory. Instead, their deficit may be more narrowly related to the degradation of visual feature knowledge associated with objects following disease in the visual association cortex. Additional work is needed to help resolve this controversy.

Logopenic variant primary progressive aphasia: is this a coherent syndrome?

The publication of the recent diagnostic criteria for PPA described three variants of PPA: naPPA, svPPA and the logopenic variant of PPA (lvPPA). Although there are some lingering controversies such as those described above, the basic outlines for naPPA and svPPA have been generally accepted. naPPA is characterized by effortful, non-fluent speech that is grammatically impoverished, although some questions remain about the precise nature of the speech disorder that can be seen in these patients: is this a disorder of motor

speech that happens to be part of a progressive form of aphasia, or are the speech errors representative of an impaired phonological system? svPPA is characterized by a deficit in semantic memory that interferes with confrontation naming and the comprehension of objects, yet the precise scope of the semantic disorder remains to be specified: is this a universal disorder of semantic impairment, or is the semantic deficit due in large part to the degradation of visuo-perceptual feature knowledge associated with object concepts?

The issues surrounding lvPPA, also known as progressive mixed aphasia, are somewhat more fundamental. This is not surprising, given the relative youth of this syndrome (Gorno-Tempini et al., 2004). lvPPA is said to be characterized by impaired confrontation naming and poor repetition in the context of relatively preserved word and object meaning and relatively preserved grammatical processing. It is clear that lvPPA differs from naPPA and svPPA. However, the core criteria for identifying lvPPA often appear to be violated. In two recent attempts to assess the reliability of the recently published PPA criteria, naPPA and svPPA have found support in independent series of patients (Leyton et al., 2011; Sajjadi et al., 2012). However, lvPPA has not been reliably supported. We address each of the criteria for lvPPA below.

Consider first the core feature of poor repetition. This is potentially useful since it is a unique disorder that can distinguish a patient with lvPPA from patients with other variants of PPA. The auditory-verbal short-term memory impairment manifests itself as difficulty repeating multisyllabic words and multiword phrases and sentences (Gorno-Tempini et al., 2008). We frequently observe patients unable to repeat words composed of as few as three syllables. Likewise, the repetition of a sequence of digits – known as digit span – is remarkably constrained to as few as two or three digits. While repetition difficulty may be a distinct feature of lvPPA, the consequences of limited auditory-verbal short-term memory are far-reaching. Other aspects of language thus may be compromised because of this limitation, and this can obscure the ability to distinguish lvPPA from other forms of PPA. For example, a limited auditory-verbal span will interfere with the comprehension of lengthy sentences. This is particularly the case for sentences that depend in part on grammatical processing since these sentences tend to be longer. It is thus necessary to assess written sentence comprehension in lvPPA to demonstrate that their sentence comprehension deficit is not one involving grammatical processing per se.

Consider next that naming difficulty is present in virtually every aphasic patient. Quantitatively, this deficit is less prominent in naPPA and is very prominent in svPPA. The presence of a naming deficit in a patient with PPA unfortunately does not help identify the subgroup with lvPPA. As the naming deficit in lvPPA worsens over time, moreover, we find that these patients often develop difficulty understanding the meanings of words as well (Etcheverry et al., 2012; Rogalski et al., 2011b). This may obscure the ability to distinguish between lvPPA and svPPA. It is necessary in this context to assess patients' understanding of object concepts, since this is impaired in svPPA but tends to be relatively preserved in lvPPA.

In sum, the syndrome of lvPPA is highly variable and elusive. Patients may have shortened utterances and relatively effortful speech related to their auditory-verbal short term memory impairment and thus resemble patients with naPPA. Alternatively, lvPPA patients have profound naming difficulty that may ultimately involve difficulty with word meaning. It is this substantial variability that may have resulted in such difficulty reliably identifying patients with lvPPA.

Conclusions

The revised diagnostic criteria for bvFTD and PPA reflect our evolving understanding of the clinical syndromes associated with frontotemporal degeneration. While standard classifications will surely benefit diagnosis and research efforts, several questions still remain. The tools and methods required to identify the insidious behavioural changes of bvFTD are still controversial. In particular, future research should explore the validity of objective, patient-based tasks that are sensitive and specific to ventromedial/orbitofrontal dysfunction. Although the basic outlines for naPPA and svPPA have been generally accepted, the scope of the semantic disorder in svPPA and the precise nature of the speech disorder in naPPA still need to be determined. Finally, lvPPA remains an elusive diagnosis, as it includes patients with variable degrees of speech and naming impairments. We hope that further research on the behavioural and language manifestations of FTLT will improve awareness and allow for adequate diagnosis and treatment of patients suffering from this devastating disorder.

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Table 1

International Consensus Criteria for bvFTD (FTDC) (adapted from Rascovsky et al., 2011).

I.	Neurodegenerative disease
A.	Patient must show progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant)
II.	Possible bvFTD
Three of the following behavioural/cognitive symptoms must be present to meet criteria	
A.	Early behavioural disinhibition
B.	Early apathy or inertia
C.	Early loss of sympathy or empathy
D.	Early perseverative, stereotyped or compulsive/ritualistic behaviour
E.	Hyperorality and dietary changes
F.	Neuropsychological profile of executive/generation deficits with relative sparing of memory and visuospatial functions
III.	Probable bvFTD
All of the following symptoms must be present to meet criteria	
A.	Meets criteria for possible bvFTD
B.	Exhibits significant functional decline (by caregiver report or functional scales)
C.	Imaging results consistent with bvFTD (i.e. frontal and/or anterior temporal atrophy on CT or MRI or frontal hypoperfusion or hypometabolism on SPECT or PET)
IV.	bvFTD with definite FTLD pathology
Criterion A and either Criterion B or C must be present to meet criteria	
A.	Meets criteria for possible or probable bvFTD
B.	Histopathological evidence of FTLD
C.	Presence of a known pathogenic mutation
V.	Exclusionary criteria for bvFTD
Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD	
A.	Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
B.	Behavioural disturbance is better accounted for by a psychiatric diagnosis
C.	Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

Table 2

Classification of PPA.

Characteristics of PPA variants				
Variant	Clinical features	Cortical atrophy	Pathology	Alternative nomenclature
svPPA	<ul style="list-style-type: none"> • Poor confrontation naming • Impaired single word comprehension • Poor object and/or person knowledge • Spared repetition; spared motor speech 	Left anterior ventral temporal lobe	<ul style="list-style-type: none"> • FTLT-TDP (~80%) 	<ul style="list-style-type: none"> • Semantic dementia
lvPPA	<ul style="list-style-type: none"> • Impaired single word retrieval • Impaired repetition of multi-syllabic words and phrases • Spared motor speech; spared single word comprehension and object knowledge; absence of agrammatism 	Left posterior temporal parietal	<ul style="list-style-type: none"> • AD (~70%) 	<ul style="list-style-type: none"> • Logopenic progressive aphasia • Progressive mixed aphasia
naPPA	<ul style="list-style-type: none"> • Effortful, halting speech with speech sound errors • Grammatical simplification and errors in language production • Impaired syntactic comprehension • Spared content word comprehension; spared object knowledge; spared repetition 	Left inferior frontal insula and anterior superior temporal	<ul style="list-style-type: none"> • FTLT-tau (~70%) 	<ul style="list-style-type: none"> • Progressive non-fluent aphasia