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Language Processing in Frontotemporal Dementia: A Brief Review

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Abstract

Frontotemporal dementia (FTD) is a neurodegenerative condition that presents with a number of distinct behavioral phenotypes. Here we review language-processing deficits in three subgroups of FTD patients: progressive nonfluent aphasia (PNFA), semantic dementia (SD), and nonaphasic FTD patients with a disorder of social and executive functioning (SOC/EXEC). These three clinical subgroups have contrasting patterns of regional cortical atrophy that can be linked to their language impairments. PNFA patients' disease includes left ventral inferior frontal cortex, resulting in impaired grammatical processing. SD patients demonstrate a profound impairment for semantic knowledge related to atrophy of the left temporal lobe. SOC/EXEC patients' frontal atrophy tends to be more right lateralized and is associated with declines in executive functioning. SOC/EXEC patients' limited executive resources impact language processing in a variety of ways, including slowed grammatical processing and impaired narrative discourse. FTD patients therefore provide converging evidence regarding dissociable components of language processing and their neuroanatomical bases.

Understanding single words requires extensive perceptual, lexical, and semantic processing (Price 1998). Comprehending a sentence poses additional requirements of knowing the rules governing relationships between words and applying these words during processing (Friederici 2002), and engaging in a conversation also depends on the ability to plan a narrative and exchange information in an organized and interactive manner with others. These processes are subserved by a distributed network of brain regions that have been elucidated largely through studies of stroke patients and functional neuroimaging in healthy adults. More recently, converging evidence regarding the neuroanatomical bases for language processing comes from patients with focal patterns of cortical atrophy, such as those observed in frontotemporal dementia (FTD).[1]

Frontotemporal dementia encompasses a spectrum of syndromes of varying etiologies that result in relatively focal damage to the frontal and temporal lobes. It occurs primarily in older adults, although its average age of onset is earlier than that of Alzheimer's disease (Haase 1977; Brun and Gustafson

1993), and it is occasionally diagnosed in adults as young as 21 years of age (Lowenberg et al. 1939). Core diagnostic features include, but are not limited to, insidious onset with slow progression, early loss of personal awareness or insight, stereotyped and perseverative behavior, impulsivity, akinesia, and a variety of declines in language function (The Lund and Manchester Groups 1994). Here, we will review language processing in three subgroups of FTD patients: progressive nonfluent aphasia (PNFA), semantic dementia (SD), and nonaphasic FTD with a disorder of social or executive functioning (SOC/EXEC) (Neary et al. 1998). The phenotypes of each of these subgroups appear to remain relatively constant over time, with declines on neuropsychological tests occurring at the same rate (Grossman et al. forthcoming). SD and PNFA patients usually fulfill the diagnostic requirements of primary progressive aphasia (Mesulam 2001; Grossman 2002), whereas SOC/EXEC patients' language disturbances are more subtle. For each subgroup of FTD patients, we summarize research findings at four stages of language processing: phonological/orthographic, semantic, grammatical, and discourse. In addition to conclusions based on stereotypical patterns of cortical atrophy, direct correlations between regional cortical atrophy and behavioral performance can be examined using voxel-based morphometry, or VBM (Ashburner and Friston 2000). VBM uses spatially normalized structural magnetic resonance image (MRI) scans to determine regions where gray matter concentration significantly differs between groups of participants (Mechelli et al. 2005). Comparing patients to a group of healthy age-matched adults in this manner can be used to determine regions of significant atrophy. Differing distributions of regional cortical atrophy in these patients provide insight into the neuroanatomic bases for their language impairments, and by inference, language processing in healthy adults. Clinically, subtype classification can also assist in differential diagnosis with other degenerative diseases such as Alzheimer's disease, and can aid in identifying the underlying pathology (Forman et al. 2006; Grossman et al. 2007), thereby affecting treatment approach.

For reference, Figure 1 displays cortical atrophy for a single patient from each FTD subgroup relative to a group of 20 healthy controls of similar age. Each patient was clinically diagnosed at the University of Pennsylvania via a consensus review mechanism using a modification of published criteria (Neary et al. 1998). Regions of significant cortical atrophy were calculated using voxel-based morphometry in SPM5 (Wellcome Trust Centre for Neuroimaging) following segmentation of gray and white matter and smoothing with a 12-mm full width at half maximum (FWHM) Gaussian kernel. Cortical atrophy, displayed in red, is significant at $P < 0.01$ (uncorrected) and encompasses at least 50 contiguous voxels. Because of individual variability in the observed distributions of atrophy, group analyses are the most informative way of delineating areas of common atrophy across each patient population (e.g. Mummery et al. 2000; Gorno-Tempini et al. 2004; Grossman et al. 2004).

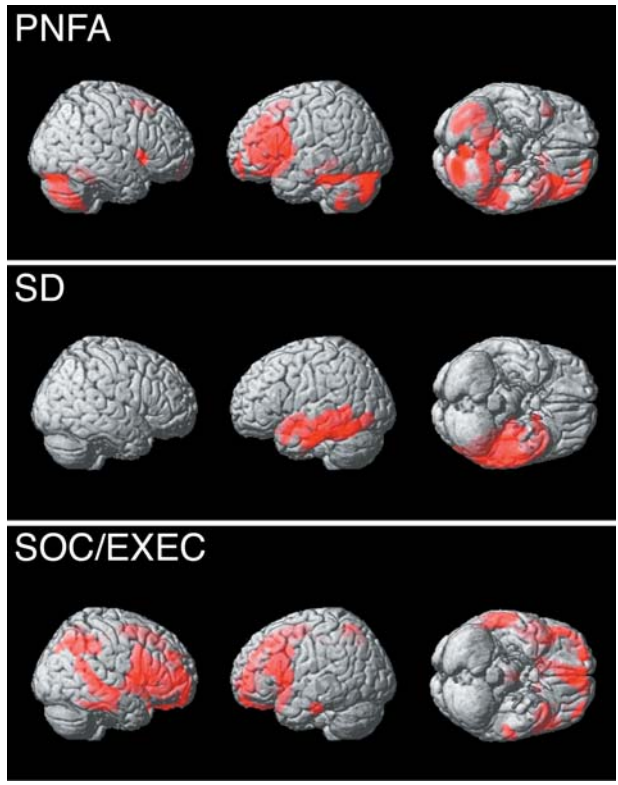

Fig. 1. Cortical atrophy in a representative patient from each FTD subgroup relative to 20 healthy adults of similar age, calculated using voxel-based morphometry with a statistical threshold of $P < 0.01$ and an extent requirement of 50 contiguous voxels. For each group, atrophy is displayed in red on right lateral, left lateral, and ventral views of a template healthy brain. With respect to language processing, these characteristic patterns of atrophy for three subgroups of FTD patients are associated primarily with grammatical and working memory deficits in PNFA patients, conceptual impairment in SD patients, and executive resource limitations in SOC/EXEC patients.

Below, we review clinical characteristics and language-processing abilities in each of the FTD subgroups. For each patient group, we relate language deficits to patterns of regional cortical atrophy.

Progressive Nonfluent Aphasia

CLINICAL PRESENTATION AND DISTRIBUTION OF CORTICAL ATROPHY IN PNFA

PNFA patients display speech that is agrammatic, dysfluent, effortful, and often dysarthric (Thompson et al. 1997; Ash et al. 2006; Josephs et al. 2006). Some executive resources, such as working memory, are affected (Libon et al. 2007). These patients show a distribution of cortical atrophy that

includes left inferior frontal cortex and proximal regions such as anterior insula, frontal operculum, dorsolateral prefrontal cortex, and anterior superior temporal cortex (Nestor et al. 2003; Gorno-Tempini et al. 2004; Grossman et al. 2004).

PHONOLOGICAL AND ORTHOGRAPHIC PROCESSING IN PNFA

Although quantitative studies are rare, PNFA patients are often reported to make phonemic errors during speech production (Weintraub et al. 1990; Snowden and Neary 1993). Caselli and Jack (1992), for example, described three patients who presented with nonfluent speech, impaired sentence repetition, and phonemic paraphasic errors, although confrontation naming was relatively good. Croot et al. (1998) examined single-word production in two PNFA patients and found high rates of phonological paraphasias in naming, reading aloud, and single-word repetition. There was some indication that phonemic errors were reduced in reading, perhaps due to orthographic cues to correct phonology. Ash et al. (2004) analyzed a semistructured speech sample in eight PNFA patients. They found that PNFA patients made paraphasic errors in 5% of their words, significantly more than SD patients and healthy controls. These errors included insertions and deletions of targets, incorrect vowel targets, and metatheses, occurring both alone and in combination.

PNFA patients may exhibit difficulty reading and some are reported to have a surface dyslexia, a condition wherein reading is mediated by direct grapheme-to-phoneme conversion, with associated impairment for orthographically irregular words (Watt et al. 1997; Noble et al. 2000). Oral reading also appears to have the same general characteristics as their spontaneous speech, and may be effortful, poorly articulated, and agrammatic, although PNFA patients' speech rate when reading aloud can be faster than production rate for spontaneous speech (Patterson et al. 2006). Apraxia of speech has been connected to cortical atrophy in left inferior frontal and bilateral superior premotor cortices (Josephs et al. 2006).

SEMANTIC PROCESSING IN PNFA

Semantic knowledge is relatively well-preserved in PNFA. Although PNFA patients' confrontation naming scores can be worse than those of healthy adults (Grossman et al. 2004), they are significantly better than SD patients'. Comprehension of single words as gauged by performance on word–picture matching tasks is also relatively preserved (Hodges and Patterson 1996), and semantic association ability as assessed through standardized measures such as the Pyramids and Palm Trees test typically remains intact until late stages of the disease (Gorno-Tempini et al. 2004). These patients nevertheless appear to have a subtle semantic impairment related to their limited executive resources (Grossman et al. 1996b; Libon et al. 2007).

In a study of concept acquisition, PNFA patients had difficulty with rule-based categorization (Koenig et al. 2006). Rule-based categorization is useful for evaluating the meaning of ambiguous objects or learning new concepts. This semantic categorization process is mediated by executive resources, including selective attention to the meaningful features of a concept, inhibiting attention to perceptually salient but otherwise less meaningful features, and maintaining the relevant features in working memory until a sufficient number has been identified to judge whether the stimulus is a member of the category.

Naming difficulties in PNFA correlate with regions of cortical atrophy in left ventral inferior frontal and insular regions, although there is also a correlation with left anterior lateral temporal regions (Grossman et al. 2004). The relationship of left ventral inferior frontal regions to naming scores may reflect a component of executive processing such as response competition selection required to select an appropriate response from several possible targets (Thompson-Schill et al. 1997).

GRAMMATICAL PROCESSING IN PNFA

Left inferior frontal cortex has long been associated with grammatical processing in studies of both stroke (Zurif et al. 1972; Zurif 1996) and functional neuroimaging (Caplan et al. 1998, 1999; Cooke et al. 2002, 2006; Fiebach et al. 2005). Consistent with these findings, PNFA patients' grammatical processing is significantly impaired. This includes tests of sentence–picture matching in which grammatical relationships in sentences are stressed (Hodges and Patterson 1996) and oral probes regarding the agent of an action in an auditory sentence comprehension task (Grossman et al. 1996b). When compared to other FTD subgroups, PNFA patients appear to show a more severe grammatical impairment than SD or SOC/EXEC patients (Snowden et al. 1992; Grossman et al. 1996b).

A potential difficulty with traditional offline measures of sentence comprehension is that patients' performance can be affected by executive resource demands of the task (e.g. decision making, remembering the sentence). One method for circumventing this difficulty is to use a task that measures online processing time, such as a target word-monitoring paradigm in which patients monitor a sentence for a target word and press a key when it occurs. When the target word occurs after an error in the sentence, normal processing is disrupted and the latency to a participant's keypress is longer. On this type of task, PNFA patients are insensitive to errors (Peelle et al. 2007) or show sensitivity to grammatical errors that is significantly delayed relative to healthy adults (Grossman et al. 2005). Grossman et al. (2005) found a significant correlation between forward digit span and offline sentence comprehension scores of sentences containing a grammatically demanding center-embedded clause, implicating working memory difficulties in PNFA patients' grammatical impairment.

Consistent with the above behavioral findings, a functional MRI (fMRI) study of sentence processing found that PNFA patients showed less inferior frontal recruitment when processing syntactically complex sentences compared to healthy seniors, but that recruitment in more dorsal frontal cortex was comparable to controls' activation pattern (Cooke et al. 2003). The type of complex object–relative center–embedded clause sentence used in this study (e.g. *The boy that the girl with the long brown hair from Boston chased is friendly*) has been shown to rely on left ventral inferior frontal areas (Cooke et al. 2002; Peelle et al. 2004). This is consistent with functional imaging studies in healthy adults that attribute syntactic processing to more ventral portions of left inferior frontal cortex and working memory functions to more dorsal portions (Cooke et al. 2002, 2006; Fiebach et al. 2005). Together, this suggests that PNFA patients' atrophy to left ventral inferior frontal cortex results in a specific impairment in grammatical processing.

DISCOURSE PROCESSING IN PNFA

The clinical impression is that conversational speech is slow and effortful in PNFA (Snowden et al. 1992; Grossman et al. 1996b; Thompson et al. 1997), although this has been assessed quantitatively only rarely. In a study of a semistructured speech sample involving narrative description of a wordless children's picture story, PNFA patients described the story content appropriately, and their narrative was otherwise well-organized. However, the speech rate of PNFA patients was about 25% of the rate of healthy adults, and half that of patients with a fluent form of progressive aphasia (Ash et al. 2006).

SUMMARY

PNFA patients have effortful speech with some phonemic processing difficulties and a differential grammatical impairment relative to other FTD subgroups. This appears to be related to damage to left inferior frontal cortex.

Semantic Dementia

CLINICAL PRESENTATION AND DISTRIBUTION OF CORTICAL ATROPHY IN SD

Patients with SD present with fluent speech that may convey relatively little information, but otherwise appears to be grammatically well-formed (Snowden and Neary 1993). SD patients' speech often contains word-finding pauses, circumlocutions, and generic or deictic expressions that substitute for concrete nouns (e.g. 'thing' or 'stuff'). Cortical atrophy in SD encompasses the ventral, lateral, and anterior temporal lobes bilaterally, although

damage in the left hemisphere tends to be more severe (Mummery et al. 2000; Gorno-Tempini et al. 2004; Grossman et al. 2004).

PHONOLOGICAL AND ORTHOGRAPHIC PROCESSING IN SD

As SD progresses, cortical atrophy typically progresses from anterior and ventral temporal areas dorsally and posteriorly. Thus, temporal areas important for phonology and reading are typically spared earlier in the disease process. Consistent with this finding, single-word repetition and auditory lexical decision ability are generally relatively preserved, although phonological errors can appear, especially for words whose meaning has been lost (Knott et al. 1997). Reilly et al. (2007) tested a cohort of four SD patients on phonetic discrimination using consonant-vowel stimuli. Performance on the phonetic discrimination task was inversely related to disease severity, with more severely impaired SD patients showing the highest discrimination accuracy. The authors interpreted this as being consistent with relatively preserved phonological processing throughout all stages of SD, but that lexical interference effects impacted the milder patients' processing. Other studies have reported that phonological processing can deteriorate in advanced SD (Jeffries et al. 2006).

Many patients with SD display surface dyslexia or surface dysgraphia, that is, difficulty pronouncing or writing irregularly spelled words, such as pronouncing *bough* to rhyme with *cough* or *trough* (Patterson and Hodges 1992; Patterson et al. 1994; Noble et al. 2000). This may indicate that semantic memory is necessary to bind sublexical elements of written words to phonological representations (Patterson and Hodges 1992; Patterson et al. 1994). Alternately, it may be that reading difficulty in SD reflects the anatomic distribution of regional atrophy, which includes ventral temporal areas important for reading.

SEMANTIC PROCESSING IN SD

As implied by its name, difficulties in semantic processing are the most pronounced feature of SD patients' language-processing difficulties (Warrington 1975; Snowden et al. 1989; Hodges et al. 1992). These semantic difficulties are seen in impoverished knowledge about features associated with word meaning (e.g. knowing a cow is an animal, but not whether it gives milk), and is seen across multiple modalities of stimulus presentation (Hodges et al. 1992, 1995; Bozeat et al. 2000). Other impairments include deficits naming to description, sorting objects based on characteristic features, and word–picture matching (Hodges and Patterson 1996; Hodges et al. 1999). This is often evidenced by significant difficulties with confrontation naming, and a tendency to substitute nonspecific words (e.g. 'thing') or superordinate categories ('animal' for 'cat') for target items (Snowden et al. 1989; Gorno-Tempini et al. 2004; Rogers et al. 2004). Naming success in

SD depends on properties of the item being named, and is positively related to age of acquisition, object familiarity, and spoken frequency (Lambon Ralph et al. 1998). These observations have been interpreted to be consistent with the claim that the semantic memory deficit in SD is due to the degradation of an amodal representation of a concept.

Other observations emphasize a selective deficit with concrete relative to abstract concepts. This 'reversal of the concreteness effect' in SD has been observed in naming (Breedin et al. 1994), and reading (Warrington and Shallice 1984). These patients are slower at naming and reading concrete nouns compared to abstract nouns, thereby reversing the common observation of greater facility on these tasks with concrete nouns. Yi et al. (2007) examined word-description matching to show reversal of the concreteness effect in SD and found the impairment was significantly more pronounced for verbs (i.e. verbs of motion compared with verbs of cognition). The authors argued that some compensation can occur for nouns that overlap in their representations and share features, but such a compensatory mechanism is less available for verbs that are less well-organized in semantic memory and therefore limited in their ability to share features. These findings are consistent with the claim that knowledge of the visual-perceptual features of a concept are preferentially degraded in SD.

The neuroanatomical basis for SD patients' semantic impairment is not completely clear. Many researchers have focused on damage to the temporal poles, particularly in the left hemisphere, as underlying semantic deficits (Rogers et al. 2004). Damage to temporal poles is often reported, and in at least one report appears to be related to performance on a semantic association task (Mummery et al. 2000). There is also some suggestion that greater atrophy in right anterior temporal regions relative to left anterior temporal regions is associated with increased comprehension difficulty (Lambon Ralph et al. 2001). Converging evidence implicating left anterior temporal regions in semantic processing comes from a recent functional neuroimaging study (Rogers et al. 2006). From this perspective, the anterior temporal region may be a multimodal convergence zone where amodal concepts are represented (Tyler et al. 2004).

Several other areas have been implicated in semantic performance in addition to anterior temporal lobes. For example, semantic association task performance has been found to correlate with the extent of disease in the left fusiform gyrus (Galton et al. 2001), a region that also shows activation during neuroimaging studies of reading and object naming in healthy adults (Moore and Price 1999; Binder et al. 2003). Confrontation naming success correlates with cortical volume in a broader region of left temporal areas, including the left temporal pole and inferolateral left temporal lobe (Galton et al. 2001; Grossman et al. 2004). Finally, Noppeney et al. (2007) compared SD patients with patients with herpes simplex virus encephalitis (HSVE). Unlike the SD patients who showed a broad semantic memory

impairment across categories, HSVE patients showed a category-specific deficit in which living things were significantly more impaired than nonliving things. The only region in which SD patients showed greater cortical atrophy than HSVE patients was on the lateral left temporal lobe, suggesting that this region may play a role in the impaired semantic processing of SD patients. Inferolateral disease in the left temporal lobe may result in disease to visual association cortex, compromising the neural representation of visual-perceptual feature knowledge. Thus, SD patients' semantic impairments are associated with left temporal damage, but more data are needed to conclusively identify the specific relationship between regional atrophy and behavior.

GRAMMATICAL PROCESSING IN SD

Patients with SD continue to produce relatively well-formed sentence structures throughout most of the course of the disease, although the content of these utterances decreases as the disease progresses (Bird et al. 2000). Sentence comprehension abilities are impaired relative to healthy adults, but they do not appear to have a specific impairment for grammatical processing. In one study that compared five SD patients to two PNFA patients, the SD patients demonstrated poorer lexical comprehension and the PNFA patients poorer sentence comprehension (Hodges and Patterson 1996). Grossman et al. (2005) investigated sentence processing using a target word-monitoring paradigm. In this task, patients pressed a button when a target word was heard; when the target word followed a grammatical error, healthy adults take longer to respond to the target word. SD patients showed a sensitivity to grammatical errors that was comparable to that of healthy adults. In context of their other impairments, SD patients' difficulty with sentence comprehension seems likely due to their deficits in semantic knowledge and lexical access, although atrophy may include left temporal areas involved in basic syntactic processing (Humphries et al. 2006).

DISCOURSE PROCESSING IN SD

Patients with SD appear to produce relatively well-formed narratives. However, the content of their narratives appears to be impoverished because of their difficulties understanding and expressing single words. Ash et al. (2006) thus showed that SD patients produce well-organized narratives that conveyed many of the essential attributes of a story. They demonstrated a reduced rate of speech and occasionally empty utterances, which were attributed to their difficulties processing the meaning of single words.

SUMMARY

Differential atrophy in the temporal lobes leads to profound semantic impairments in SD patients, with input phonologic processing (i.e. speech

perception) and output phonological processing (i.e. phonological encoding and speech production) impacted to a lesser degree. SD patients do not show a differential impairment with grammatical or discourse processing, but their difficulty with semantic knowledge and lexical access results in lower overall sentence comprehension ability and poorer narrative expression.

Nonaphasic FTD (SOC/EXEC)

CLINICAL PRESENTATION AND DISTRIBUTION OF CORTICAL ATROPHY IN SOC/EXEC

Clinical presentation of SOC/EXEC patients is most notable for their unusual and often bizarre changes in social comportment and personality, including inflexibility, apathy, impulsivity, a lack of inhibition, and lack of empathy (Gustafson 1987, 1993; Miller et al. 1997; Liu et al. 2004), and are often characterized as being aggressive or socially disruptive. They also exhibit deficits of executive functioning (Rahman et al. 1999; Libon et al. 2007). Unlike PNFA and SD, language deficits are not considered a defining aspect of the diagnosis, and so studies of language processing in SOC/EXEC patients are rare. Nevertheless, these patients do have considerably difficulty on language-mediated tasks, apparently reflecting the declines in executive functioning that also appear to compromise language. SOC/EXEC patients demonstrate atrophy in the temporal and frontal lobes, including the insula; frontal atrophy is more right lateralized and rarely involves inferior frontal regions affected in PNFA (Rosen et al. 2002, 2005; Grossman et al. 2004).

PHONOLOGICAL AND ORTHOGRAPHIC PROCESSING IN SOC/EXEC

Phonemic fluency in SOC/EXEC patients, assessed by generation of words beginning with a target letter, is comparable to that in SD (Rosen et al. 2002; Libon et al. 2007). In SD patients, this impairment likely stems from difficulties with access and representation of word forms in the mental lexicon, whereas in SOC/EXEC patients it can be attributed to executive demands of the task such as performing an organized search through the mental lexicon and keeping track of previously mentioned words in working memory so that these are not repeated.

SEMANTIC PROCESSING IN SOC/EXEC

SOC/EXEC patients are less impaired than SD patients on traditional measures of semantic memory, assessed using tasks such as naming, category fluency, word–picture matching, picture sorting, and semantic feature questions (Hodges et al. 1999; Libon et al. 2007). Nevertheless, there are executive deficits in SOC/EXEC patients that may contribute to more subtle semantic processing difficulties. As in patients with PNFA, SOC/EXEC

patients appear to have a disorder of rule-based semantic categorization, where the meaning of ambiguous concepts depends on executive resources to sort out the true meaning of a word or object (Koenig et al. 2006).

The component of verb meaning related to thematic matrix (who does what to whom) appears to be very fragile in SOC/EXEC patients. During acquisition of a novel verb, Murray et al. (2007) showed that SOC/EXEC patients are modestly impaired in their ability to acquire semantic and grammatical components of the new verb. However, these patients were disproportionately compromised learning about the thematic properties of the new verb. The authors reasoned that a thematic matrix may be an emergent property of a verb that is derived from the integration of its grammatical and semantic properties, and that SOC/EXEC patients may have difficulty with this resource-based integration process. More generally, verbs appear to have greater resource demands than nouns, perhaps related to the large amount of grammatical and thematic knowledge featured in this word class compared to nouns. Correspondingly, Rhee et al. (2001) showed that difficulty on a word–picture matching task was disproportionately compromised for verbs relative to nouns during simultaneous performance of a secondary task.

Naming difficulty in SOC/EXEC patients has been shown to correlate with regions of atrophy in the left anterior temporal lobe and the right dorsolateral prefrontal cortex (Grossman et al. 2004).

GRAMMATICAL PROCESSING IN SOC/EXEC

Although not typically as impaired as SD or PNFA patients, SOC/EXEC patients' sentence comprehension is worse than that of healthy controls (Grossman et al. 1996a). Grossman et al. (2005) assessed the time course of grammatical processing using a target word-monitoring paradigm. The authors found that SOC/EXEC patients show sensitivity to grammatical violations in the same short time window as healthy adults. However, unlike healthy adults, their sensitivity extended into a delayed time window, suggesting that grammatical processing took significantly longer to complete. Their comprehension difficulty correlated with tasks that reflect executive functioning such as backward digit span, suggesting an executive cause for the sentence-comprehension impairment.

These data suggest that SOC/EXEC patients have difficulty with processing grammatical information, but that this difficulty is not due to the type of grammar-specific impairment observed in PNFA patients. Rather, for SOC/EXEC patients, executive resource limitations appear to hinder grammatical processing. Consistent with this view, an fMRI study of sentence comprehension showed that SOC/EXEC patients are able to recruit ventral portions of left inferior frontal cortex comparably to healthy controls, but had more difficulty recruiting dorsal regions of left inferior frontal cortex associated with working memory (Cooke et al. 2003).

DISCOURSE PROCESSING IN SOC/EXEC

Whereas subtle deficits in grammatical and semantic processing may become evident in SOC/EXEC patients, the most obvious language deficit in SOC/EXEC relates to conversational discourse. Narrative speech often rambles into unrelated topics, and responses to questions in the course of a conversation may be quite tangential. This is due to a disorder of discourse that results from their limited executive resources. Ash et al. (2006) showed that SOC/EXEC patients are reasonably accurate at describing individual events illustrated in a wordless picture story, but that they have profound difficulty assembling these events into a coherent story. They demonstrated significant difficulty establishing local connectedness between successive events in a story, and had difficulty maintaining the theme of the story throughout the course of its expression. Likewise, the overall point of the story was lost to the majority of the SOC/EXEC patients. It is striking that this deficit in discourse was much more pronounced in SOC/EXEC patients than patients with a progressive form of aphasia.

SOC/EXEC patients also appear to have difficulty understanding extended narratives (Consentino et al. 2006). Patients were given four-sentence scripts describing familiar activities such as 'going fishing'. Half of the scripts had an error that patients were asked to detect, including either an error in the order of event occurrence within the script (e.g. placing a worm on the hook after the hook had been tossed into the water) or an error in a fact within an event (e.g. placing a flower on the hook instead of a worm). This study showed significant difficulty appreciating the order in which events are organized in a script, although there was less difficulty detecting factual errors. Difficulty detecting organizational errors in SOC/EXEC patients correlated with performance on measures of executive functioning.

Deficits in discourse may be related to a disorder of social cognition seen in SOC/EXEC patients. Studies of Theory of Mind in SOC/EXEC show profound impairments in judging the thoughts and intentions of others (Rahman et al. 1999). In a recent study examining social judgments in SOC/EXEC patients (e.g. how to respond to finding a fly in your soup in a restaurant), Eslinger et al. (2007) showed that these patients have significant difficulty determining the most appropriate outcome of social challenges. This was related to an impairment on executive measures involving mental flexibility. Performance correlated with cortical atrophy in right frontal and temporal regions.

SUMMARY

SOC/EXEC patients' most prominent clinical features include disorders of social and executive functioning. Their executive dysfunction contributes to language impairments, including impaired naming and sentence

comprehension scores relative to healthy adults and prominent deficits in discourse processing.

Conclusions

Differing distributions of regional cortical atrophy lead to distinct language-processing impairments in patients with FTD. The few studies devoted to phonologic and orthographic processing suggest that this aspect of language is fairly well-preserved in all subgroups, although PNFA patients have phonemic paraphasic errors in their speech and phonological processing may be affected in later stages of SD. Semantic knowledge is differentially affected in SD due to atrophy of the temporal lobe, but is relatively intact in PNFA and SOC/EXEC patients. Of all FTD subgroups, PNFA patients demonstrate the most severe grammatical processing impairments due to left ventral inferior frontal atrophy; SD and SOC/EXEC patients, although impaired in sentence comprehension relative to healthy adults, do not show a differential impairment for grammatically complex sentences. Disorders of discourse are profoundly compromised in SOC/EXEC patients, with patients with a progressive form of aphasia less compromised with this aspect of language. In principle, it is possible that patients accomplish language-processing tasks using a different set of neuroanatomical resources from that of healthy adults (Price and Friston 2002). However, the correspondence between activation studies in healthy adults and the regional distributions of anatomy in the FTD subgroups suggest that this is not the case. FTD patients thus provide an ideal population in which to test hypotheses about dissociable neuroanatomical resources involved in grammatical, semantic, and discourse aspects of language processing.

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Short Biography

Jonathan Peelle obtained his PhD in neuroscience from Brandeis University, and is currently in the Department of Neurology at the University of Pennsylvania. His research focuses on language processing and cortical plasticity in healthy aging and neurodegenerative disease.

Murray Grossman (MD, EdD) trained initially at the Aphasia Research Center of Boston University and the Boston Veterans Administration Medical Center. After a postdoctoral fellowship in the Department of

Brain and Cognitive Sciences at Massachusetts Institute of Technology, he attended medical school at McGill University's Faculty of Medicine. His training in neurology was at the University of Pennsylvania, where he is currently on staff.

Notes

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[1] This family of diseases is also referred to as 'frontotemporal lobar degeneration', with 'frontotemporal dementia' being reserved for the nonaphasic clinical presentation. We follow the convention of referring to the full spectrum of cases as FTD (McKhann et al. 2001), in large part because lobar atrophy is not always apparent in imaging studies.

Works Cited

Ash, Sharon, Peachie Moore, S. Antani, G. McCawley, Melissa Work, and Murray Grossman. 2006. Trying to tell a tale: discourse impairments in progressive aphasia and frontotemporal dementia. Neurology 66.1405–13.

Ash, Sharon, Peachie Moore, R. Hauck, S. Antani, J. Katz, and Murray Grossman. 2004. Quantitative analysis of paraphasic errors in frontotemporal dementia. Neurology 62.A166.

Ashburner, John, and Karl J. Friston. 2000. Voxel-based morphometry – The methods. NeuroImage 11.805–21.

Binder, Jeffrey R., K. A. McKiernan, M. E. Parsons, C. F. Westbury, Edward T. Possing, J. N. Kaufman, and L. Buchanan. 2003. Neural correlates of lexical access during visual word recognition. Journal of Cognitive Neuroscience 15.373–93.

Bozeat, Sasha, Matthew A. Lambon Ralph, Karalyn Patterson, Peter Garrard, and John R. Hodges. 2000. Non-verbal semantic impairment in semantic dementia. Neuropsychologia 38.1207–15.

Breedin, Sarah D., Eleanor M. Saffran, and H. Branch Coslett. 1994. Reversal of the concreteness effect in a patient with semantic dementia. Cognitive Neuropsychology 11.617–60.

Brun, Arne, and Lars Gustafson. 1993. The Lund longitudinal dementia study: A 25 year perspective on neuropathology, differential diagnosis, and treatment. Alzheimer's disease: advances in clinical and basic research, ed. by B. Corain, K. Iqbal, M. Nicolini, B. Winblad, H. Wisniewski, P. Zatta, 3–18. London: John Wiley & Sons.

Caplan, David, Nathaniel Alpert, and Gloria Waters. 1998. Effects of syntactic structure and propositional number on patterns of regional cerebral blood flow. Journal of Cognitive Neuroscience 10.541–52.

——. 1999. PET studies of syntactic processing with auditory sentence presentation. NeuroImage 9.343–51.

Caselli, Richard J., and Clifford R. Jack. 1992. Asymmetric cortical degeneration syndromes: a proposed clinical classification. Archives of Neurology 49:770–9.

Consentino, Stephanie, Douglas Chute, David Libon, Peachie Moore, and Murray Grossman. 2006. How does the brain support script comprehension? A study of executive processes and semantic knowledge in dementia. Neuropsychology 20.307–18.

Cooke, Ayanna, Chris DeVita, James Gee, David Alsop, John Detre, Willis Chen, and Murray Grossman. 2003. Neural basis for sentence comprehension deficits in frontotemporal dementia [May]. Brain and Language 85.211–21.

Cooke, Ayanna, Murray Grossman, C. DeVita, J. Gonzalez-Atavales, Peachie Moore, W. Chen, J. Gee, and John Detre. 2006. Large-scale neural network for sentence processing. Brain and Language 96.14–36.

Cooke, Ayanna, Edgar B. Zurif, Christian DeVita, David Alsop, Phyllis Koenig, John Detre, James Gee, Maria Pinango, Jennifer Balogh, and Murray Grossman. 2002. Neural basis

for sentence comprehension: Grammatical and short-term memory components. Human Brain Mapping 15.80–94.

Croot, Karen, Karalyn Patterson, and John R. Hodges. 1998. Single word production in nonfluent progressive aphasia. Brain and Language 61.226–73.

Eslinger, Paul J., Peachie Moore, Vanessa Troiani, Shweta Antani, Katy Cross, Shaleigh Kwok, and Murray Grossman. 2007. OOPS! Resolving social dilemmas in frontotemporal dementia. Journal of Neurology, Neurosurgery, and Psychiatry 78.457–60.

Fiebach, Christian J., Matthias Schlesewsky, G. Lohmann, D. Yves von Cramon, and Angela D. Friederici. 2005. Revisiting the role of Broca's area in sentence processing: Syntactic integration versus syntactic working memory. Human Brain Mapping 24.79–91.

Forman, Mark S., Jennifer Farmer, Julene K. Johnson, Christopher M. Clark, Steven E. Arnold, H. Branch Coslett, Anjan Chatterjee, Howard I. Hurtig, Jason H. Karlawish, Howard J. Rosen, Vivianna Van Deerlin, Virginia M.-Y. Lee, Bruce L. Miller, John Q. Trojanowski, and Murray Grossman. 2006. Frontotemporal dementia: clinicopathological correlations. Annals of Neurology 59.952–62.

Friederici, Angela D. 2002. Towards a neural basis of auditory sentence processing. Trends in Cognitive Sciences 6.78–84.

Galton, Clare J., Karalyn Patterson, K. Graham, Matthew A. Lambon Ralph, G. Williams, N. Antoun, B. J. Sahakian, and J. R. Hodges. 2001. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. Neurology 57.216–25.

Gorno-Tempini, Maria Luisa, Nina F. Dronkers, Katherine P. Rankin, Jennifer M. Ogar, La Phengrasamy, Howard J. Rosen, Julene K. Johnson, Michael W. Weiner, and Bruce L. Miller. 2004. Cognition and anatomy in three variants of primary progressive aphasia. Annals of Neurology 55.335–46.

Grossman, Murray. 2002. Progresive aphasic syndromes: clinical and theoretical advances. Current Opinion in Neurology 15.409–13.

Grossman, Murray, Mark D'Esposito, E. Hughes, K. Onishi, N. Biassou, T. White-Devine, and K. M. Robinson. 1996a. Language comprehension profiles in Alzheimer's disease, multi-infarct dementia, and frontotemporal degeneration. Neurology 47.183–9.

Grossman, Murray, J. Mickanin, K. Onishi, E. Hughes, Mark D'Esposito, X.-S. Ding, A. Alavi, and M. Reivich. 1996b. Progressive non-fluent aphasia: language, cognitive and PET measures contrasted with probable Alzheimer's disease. Journal of Cognitive Neuroscience 8.135–54.

Grossman, Murray, Corey McMillan, Peachie Moore, Lijun Ding, Guila Glosser, Melissa Work, and James Gee. 2004. What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. Brain 127.628–49.

Grossman, Murray, David J. Libon, Mark S. Forman, Lauren Massimo, Elisabeth Wood, Peachie Moore, Chivon Anderson, Jennifer Farmer, Anjan Chatterjee, Christopher M. Clark, H. Branch Coslett, Howard I. Hurtig, Virginia M.-Y. Lee, and John Q. Trojanowski. 2007. Distinct antemortem profiles in pathologically-defined patients with frontotemporal dementia. Archives of Neurology 64.1601–09.

Grossman, Murray, Sharon X. Xie, David J. Libon, Xingmei Wang, Lauren Massimo, Peachie Moore, Luisa Vesely, Rebecca Berkowitz, Anjan Chatterjee, H. Branch Coslett, Howard I. Hurtig, Mark S. Forman, Virginia M.-Y. Lee, and John Q. Trojanowski. forthcoming 2008. Longitudinal decline in autopsy-defined frontotemporal dementia. Neurology.

Grossman, Murray, Jina Rhee, and Peachie Moore. 2005. Sentence processing in frontotemporal dementia. Cortex 41.764–77.

Gustafson, Lars. 1987. Frontal lobe degeneration of the non-Alzheimer type. II. Clinical picture and differential diagnosis. Archives of Gerontology and Geriatrics 6.209–23.

——. 1993. Clinical picture of frontal lobe degeneration of non-Alzheimer type. Dementia 4.143–8.

Haase, G. R. 1977. Diseases presenting as dementia. Dementia, ed. by C. E. Wells, 27–67. Philadelphia, PA: F. A. Davis.

Hodges, John R., and Karalyn Patterson. 1996. Nonfluent progressive aphasia and semantic dementia: A comparative neuropsychological study. Journal of the International Neuropsychological Society 2.511–24.

Hodges, John R., N. Graham, and Karalyn Patterson. 1995. Charting the progression in semantic dementia: implications for the organisation of semantic memory. Memory 3.463–95.

Hodges, John R., Karalyn Patterson, Susan Oxbury, and Elaine Funnell. 1992. Semantic Dementia: Progressive fluent aphasia with temporal lobe atrophy. Brain 115.1783–806.

Hodges, John R., Karalyn Patterson, Richard Ward, Peter Garrard, Thomas Bak, Richard Perry, and Carol Gregory. 1999. The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. Neuropsychology 13.31–40.

Humphries, Colin, Jeffrey R. Binder, David A. Medler, and Einat Liebenthal. 2006. Syntactic and semantic modulation of neural activity during auditory sentence comprehension. Journal of Cognitive Neuroscience 18.665–79.

Jeffries, Elizabeth, Karalyn Patterson, and Matthew A. Lambon Ralph. 2006. The natural history of late-stage 'pure' semantic dementia. Neurocase 12.1–14.

Josephs, Keith A., Joseph R. Duffy, Edyth A. Strand, Jennifer L. Whitwell, Kenneth F. Layton, Joseph E. Parisi, Mary F. Hauser, Robert J. Witte, Bradley F. Boeve, David S. Knopman, Dennis W. Dickson, Clifford R. Jack Jr., and Ronald C. Peterson. 2006. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain 129.1385–98.

Knott, Raymond, Karalyn Patterson, and John R. Hodges. 1997. Lexical and semantic binding effects in short-term memory. Cognitive Neuropsychology 14.1165–216.

Koenig, Phyllis, Edward E. Smith, and Murray Grossman. 2006. Semantic categorisation of novel objects in frontotemporal dementia. Cognitive Neuropsychology 23.541–62.

Lambon Ralph, Matthew A., Kim S. Graham, Andrew W. Ellis, and J. R. Hodges. 1998. Naming in semantic dementia – what matters? Neuropsychologia 36.775–84.

Lambon Ralph, Matthew A., James L. McClelland, Karalyn Patterson, Clare J. Galton, and John R. Hodges. 2001. No right to speak? The relationship between object naming and semantic impairment: Neuropsychological evidence and a computational model. Journal of Cognitive Neuroscience 13.341–56.

Libon, David J., S. X. Xie, Peachie Moore, J. Farmer, Shweta Antani, Gwyneth McCawley, Katy Cross, and Murray Grossman. 2007. Patterns of neuropsychological impairment in frontotemporal dementia. Neurology 68.369–75.

Liu, W., Bruce L. Miller, Joel H. Kramer, K. Rankin, C. Wyss-Coray, R. Gearhart, L. Phengrasamy, M. Weiner, and Howard J. Rosen. 2004. Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. Neurology 62.742–8.

Lowenberg, K., D. A. Boyd, and D. D. Salon. 1939. Occurrence of Pick's disease in early adult years. Archives of Neurology and Psychiatry 41.1004–20.

McKhann, Guy, John Q. Trojanowski, Murray Grossman, Bruce L. Miller, Dennis Dickson, and Marilyn Albert. 2001. Clinical and pathological diagnosis of frontotemporal dementia: Report of a work group on frontotemporal dementia and Pick's disease. Archives of Neurology 58:1803–9.

Mechelli, Andrea, Cathy J. Price, Karl J. Friston, and John Ashburner. 2005. Voxel-based morphometry of the humain brain: Methods and applications. Current Medical Imaging Reviews 1.105–13.

Mesulam, M. Marsel. 2001. Primary progressive aphasia. Annals of Neurology 49.425–32.

Miller, Bruce L., A. Darby, D. F. Benson, J. L. Cummings, and M. H. Miller. 1997. Aggressive, socially disruptive and antisocial behaviour associated with fronto-temporal dementia. The British Journal of Psychiatry 170.150–4.

Moore, Caroline J., and Cathy J. Price. 1999. Three distinct ventral occipitotemporal regions for reading and object naming. NeuroImage 10.181–92.

Mummery, Cath J., Karalyn Patterson, Cathy J. Price, John Ashburner, Richard S. J. Frackowiak, and John R. Hodges. 2000. A voxel-based morphometry study of Semantic Dementia: Relationship between temporal lobe atrophy and semantic memory. Annals of Neurology 47.36–45.

Murray, Ryan, Phyllis Koenig, Shweta Antani, Gwyneth McCawley, and Murray Grossman. 2007. Lexical acquisition in progressive aphasia and frontotemporal dementia. Cognitive Neuropsychology 24.48–69.

Neary, David, Julie S. Snowden, Lars Gustafson, Ulla Passant, Donald Stuss, S. Black, M.

Freedman, Andrew Kertesz, P. H. Robert, Marilyn Albert, K. Boone, Bruce L. Miller, J. Cummings, and D. F. Benson. 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51.1546–54.

Nestor, Peter J., Naida L. Graham, Tim D. Fryer, Guy B. Williams, Karalyn Patterson, and John R. Hodges. 2003. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. Brain 126.2406–18.

Noble, Kimberly, Guila Glosser, and Murray Grossman. 2000. Reading in dementia. Brain and Language 74.48–69.

Noppeney, Uta, Karalyn Patterson, Lorraine K. Tyler, Helen Moss, Emmanuel A. Stamatakis, Peter Bright, C. Mummery, and Cathy J. Price. 2007. Temporal lobe lesions and semantic impairment: A comparison of herpes simplex virus encephalitis and semantic dementia. Brain 130.1138–47.

Patterson, Karalyn, and John R. Hodges. 1992. Deterioration of word meaning: Implications for reading. Neuropsychologia 30.1025–40.

Patterson, Karalyn, N. Graham, and John R. Hodges. 1994. The impact of semantic memory loss on phonologic representations. Journal of Cognitive Neuroscience 6.57–69.

Patterson, Karalyn, Naida L. Graham, Matthew A. Lambon Ralph, and John R. Hodges. 2006. Progressive non-fluent aphasia is not a progressive form of non-fluent (post-stroke) aphasia. Aphasiology 20.1018–34.

Peelle, Jonathan E., Ayanna Cooke, Peachie Moore, Luisa Vesely, and Murray Grossman. 2007. Syntactic and thematic components of sentence processing in progressive nonfluent aphasia and nonaphasic frontotemporal dementia. Journal of Neurolinguistics 20.482–94.

Peelle, Jonathan E., Corey McMillan, Peachie Moore, Murray Grossman, and Arthur Wingfield. 2004. Dissociable patterns of brain activity during comprehension of rapid and syntactically complex speech: Evidence from fMRI. Brain and Language 91.315–25.

Price, Cathy J. 1998. The functional anatomy of word comprehension and production. Trends in Cognitive Sciences 2.281–8.

Price, Cathy J., and Karl J. Friston. 2002. Degeneracy and cognitive anatomy. Trends in Cognitive Sciences 6.416–21.

Rahman, Shibley, Barbara J. Sahakian, John R. Hodges, Robert D. Rogers, and Trevor W. Robbins. 1999. Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 122.1469–93.

Reilly, Jamie, Katy Cross, Vanessa Troiani, and Murray Grossman. 2007. Single-word semantic judgements in semantic dementia: Do phonology and grammatical class count? Aphasiology 21.558–69.

Rhee, Jina, P. Antiquena, and Murray Grossman. 2001. Verb comprehension in frontotemporal degeneration: the role of grammatical, semantic and executive components. Neurocase 7.173–84.

Rogers, Timothy T., Julia Hocking, Uta Noppeney, Andrea Mechelli, Maria Luisa Gorno-Tempini, Karalyn Patterson, and Cathy J. Price. 2006. Anterior temporal cortex and semantic memory: Reconciling findings from neuropsychology and functional imaging. Cognitive, Affective, and Behavioral Neuroscience 6.201–3.

Rogers, Timothy T., Matthew A. Lambon Ralph, Peter Garrard, Sasha Bozeat, James L. McClelland, John R. Hodges, and Karalyn Patterson. 2004. Structure and deterioration of semantic memory: A neuropsychological and computational investigation. Psychological Review 111.205–35.

Rosen, Howard J., Stephen C. Allison, Guido F. Schauer, Maria Luisa Gorno-Tempini, Michael W. Weiner, and Bruce L. Miller. 2005. Neuroanatomical correlates of behavioural disorders in dementia. Brain 128.2612–25.

Rosen, Howard J., Maria Luisa Gorno-Tempini, W. P. Goldman, R. J. Perry, N. Schuff, Michael Weiner, R. Feiwell, J. H. Kramer, and Bruce L. Miller. 2002. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 58.198–208.

Snowden, Julie S., and David Neary. 1993. Progressive language dysfunction and lobar atrophy. Dementia 4.226–31.

Snowden, Julie S., P. J. Goulding, and David Neary. 1989. Semantic dementia: A form of circumscribed cerebral atrophy. Behavioural Neurology 2.167–82.

Snowden, Julie S., David Neary, D. M. Mann, P. J. Goulding, and H. J. Testa. 1992. Progressive language disorder due to lobar atrophy. Annals of Neurology 31.174–83.

The Lund and Manchester Groups. 1994. Clinical and neuropathological criteria for frontotemporal dementia. Journal of Neurology, Neurosurgery, and Psychiatry 57.416–18.

Thompson, C. K., K. J. Ballard, M. E. Tait, S. Weintraub, and M. Mesulam. 1997. Patterns of language decline in non-fluent primary progressive aphasia. Aphasiology 11.297–331.

Thompson-Schill, Sharon L., Mark D'Esposito, Geoffrey K. Aguirre, and Martha J. Farah. 1997. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. Proceedings of the National Academy of Sciences, USA 94.14792–7.

Tyler, Lorraine K., Emmanuel A. Stamatakis, Peter Bright, K. Acres, S. Abdallah, J. M. Rodd, and H. E. Moss. 2004. Processing objects at different levels of specificity. Journal of Cognitive Neuroscience 16.351–62.

Warrington, Elizabeth K. 1975. The selective impairment of semantic memory. Quarterly Journal of Experimental Psychology 27.635–57.

Warrington, Elizabeth K., and Tim Shallice. 1984. Category specific semantic impairments. Brain 104.829–54.

Watt, Susan, Regina Jokel, and Marlene Behrmann. 1997. Surface dyslexia in nonfluent progressive aphasia. Brain and Language 56.211–33.

Weintraub, Sandra, N. P. Rubin, and M. Marsel Mesulam. 1990. Primary progressive aphasia. Longitudinal course, neuropsychological profile, and language features. Archives of Neurology 47.1329–35.

Yi, Hyon-Ah, Peachie Moore, and Murray Grossman. 2007. Reversal of the concreteness effect for verbs in patients with semantic dementia. Neuropsychology 21.9–19.

Zurif, Edgar B. 1996. Brain regions of relevance to syntactic processing. An invitation to cognitive science, ed. by D. Osherson, 381–97. Cambridge, MA: MIT Press.

Zurif, Edgar B., Alfonso Caramazza, and R. Myerson. 1972. Grammatical judgments of agrammatic aphasics. Neuropsychologia 10.405–17.

