Primer of Behavioral Neurology course: Language

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This lecture will cover the cognitive and neural basis of common language disturbances with particular emphasis on progressive language disorders that are caused by focal neurodegenerative diseases. The following disturbances will be discussed: apraxia of speech, agrammatism, phonological loop disorders, semantic deficits and anomia. Ways of assessing these deficits at the bedside will be provided.

Apraxia of speech

Apraxia of speech (AOS) has emerged as the term to describe a motor speech disorder characterized by an impaired ability to coordinate the sequential, articulatory movements necessary to produce speech sounds [1]. Vascular brain lesions are the most common cause of AOS, but the disorder may also result from tumors and trauma. Often AOS has also been identified as the first symptom of neurodegenerative diseases as in non-fluent/agrammatic primary progressive aphasia (nfvPPA)[2,3]. In recent years, progressive speech decline has been described as the initial and primary symptom in a number of degenerative cases[4-7].

Darley first described AOS as "a disorder of motor speech programming manifested primarily by errors of articulation" [8]. He noted that AOS resulted from "an impaired ability to program the positioning of the speech musculature… and the sequencing of speech musculature". Articulatory errors and prosodic abnormalities are hallmarks of AOS. Prosodic deficits, however, are thought to be a secondary effect of poor articulation (e.g., patients may speak in a slow, halting manner because they are anticipating difficulty speaking) [8]. Patients with AOS may present with any or all of the following salient signs: 1) effortful trial and error groping with attempts at self-correction often with distorted sounds; 2) persistent dysprosody (abnormal rhythm, stress and intonation); 3) articulatory inconsistency on repeated productions of the same utterance and/or 4) obvious difficulty initiating utterances [1]. These characteristic deficits have traditionally been elicited in clinical settings with the administration of the Motor Speech Evaluation (MSE), which includes a collection of words, phrases and sentences that are particularly sensitive to AOS [1]. Errors are more common on multisyllabic words and on consonant clusters, rather than singleton consonants (e.g. 'strict' will be more difficult 'sit').

When diagnosing AOS, it is important to distinguish the disorder from Broca's aphasia, conduction aphasia and dysarthria. The term 'apraxia of speech' has occasionally been used synonymously with Broca's aphasia. The misconception that the two disorders are one in the same may have arisen from the fact that AOS and Broca's aphasia often occur together [9]. However, the two disorders have been shown to be distinguishable, since AOS has been documented in non-aphasic patients, who do not manifest truly linguistic deficits, such as agrammatism and naming deficits.

AOS is often confused with conduction aphasia, perhaps because sound level errors (substitutions, additions, transpositions or omissions) are prominent in both disorders. However, the nature of errors is thought to be different[9]. The sound errors in conduction aphasia reflect an underlying deficit in the selection of the phonemes for speech, i.e. a language deficit. Apraxic speakers, on the other hand, are believed to select the correct phonemes, only to have trouble with their motor execution. Wertz has suggested that patients with conduction aphasia typically speak with near normal prosody, whereas halting, effortful speech with abnormal prosody is considered a hallmark of AOS[1,10]. Despite this, the differential diagnosis of the speech production

errors in AOS and conduction aphasia can be difficult given the similarity in sound level errors. In progressive aphasia AOS is a common early symptom in the nonfluent/agrammatic variant (nfvPPA)[2,3,7,11]while sound level errors are typical of the logopenic variant[12]. When AOS is the predominant clinical feature, the term “progressive apraxia of speech” has been used[13].

AOS differs from dysarthria in that dysarthria is caused by impairment of muscle strength, tone, range of motion and/or coordination, while AOS is not caused by these impairments. Dysarthria can affect phonation, resonance, articulation or prosody as the result of damage to the central or peripheral nervous system [8]. Also, the errors heard in dysarthric speech are typically consistent and predictable, while the speech errors heard in AOS tend to be highly irregular [8,9]. Spastic dysarthria and AOS might be common features in nfvPPA who have FTLD-TDPA pathology[14]

Pinpointing a singular brain region associated with AOS has been controversial. The disorder has been described in patients with lesions to Broca’s area[15], left frontal and temporoparietal cortex[16], the left, superior, anterior region of the insula [17], as well as left subcortical structures, particularly within the basal ganglia [9,18].

Dronkers compared 25 left hemisphere stroke patients with chronic AOS to 19 patients without AOS and found that all patients with AOS shared a common site of lesion within the precentral gyrus of the left anterior insula[17]. None of the 19 patients with an infarction of the left MCA without AOS had lesions in this same region. This disassociation provided strong evidence that lesions to the anterior insula area may result in AOS.

Other studies have argued against a relationship between the insula and AOS. In a study with 80 acute stroke patients, Hillis used diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) in acute patients within the first 24 hours of stroke and found no association between AOS and metabolism in the left insula[15]. AOS was instead associated with structural damage or low blood flow in the left posterior inferior frontal gyrus. Variations in stage of illness and techniques used may account for these differences.

AOS has also been reported in patients with subcortical damage. Kertesz reported 10 cases of patients with AOS and aphasia who had lesions in the basal ganglia and internal capsule[19]. Closer inspection of CT scans provided with these cases reveal insular involvement as well. Peach and Tonkovich recently described the phonemic characteristics of AOS in a patient with subcortical damage as the result of a hemorrhage[18]. Though there may be some disagreement as to precise location, accounts of AOS in neurodegenerative cases has demonstrated that patients with progressive non-fluent/agrammatic aphasia and AOS showed focal atrophy in all three of the regions mentioned above, including the left frontal operculum, left insula and subcortical regions[20]. In a recent study, Wilson and colleagues showed that in primary progressive aphasia number of distortion errors, typical of AOS, were correlated with white matter volumes in the left frontal lobe. Phonological errors were instead associated with posterior-temporal gray matter volumes[12].

Agrammatism

Grammar refers to a set of rules dealing with syntax (word order) and word structure (morphology) of a language. Syntactic processing is a complex cognitive function whereby speakers and listeners implicitly construct and manipulate abstract hierarchical structures that specify the relationships between the words and morphemes that make up sentences. Neuropsychological and functional neuroimaging studies have shown that brain regions throughout dominant perisylvian cortex are involved in syntax[21,22]. A particularly important region

is the posterior inferior frontal gyrus (IFG), also known as Broca's area[23-27]. Numerous functional imaging studies have revealed increased inferior frontal activation for syntactically complex sentences relative to simpler ones[28,29]. Patients with damage to this region often present with Broca's aphasia, which is characterized by expressive and receptive agrammatism. Expressive agramamtism is characterized by misuse or absence of functor words, such as pronouns and articles and morphological errors, such as misuse of verb inflections[22,30-32]. Simple tasks such as a picture description can be used to identify expressive agramamtism[27,33]. In mild cases, tests of constrained sentence production might be necessary to identify the deficit. The Goodglass story completion test is a classic example of such task[34,32]. The examiner orally presents a simple story of two or three sentences designed to elicit a predictable target sentence or phrase. For example, the lead-in "A baby has a toy. I take the toy away. What happens?" targets a third person singular present verb form, e.g. "the baby cries" or "he cries". Receptive agrammatism is instead characterized by an impairment in comprehension of complex syntactical structures[26,27,35,36]. In English the most common and "easy" sentence type follows the basic subject-verb-object ("canonical") word order (e.g., *The girl is pushing the boy*). Sentences with non-canonical word order, such as passive sentences, do not follow this particular rule (e.g., *The girl is being pushed by the boy*) and are generally considered to be more complex and more difficult to understand. Sentence comprehension tasks need to include these kind of complex sentences if they aim at identifying agrammatism.

In nfvPPA degeneration of inferior frontal cortex has been associated with prominent syntactic deficits[37,38]. NfvPPA patients produce agrammatic speech, are impaired in comprehending syntactically complex sentences, and are relatively insensitive to grammatical violations[39]. Structural imaging studies using voxel-based morphometry have demonstrated associations between left inferior frontal volume loss and both receptive and expressive syntactic deficits.

Unlike stroke-induced Broca's aphasia in which the IFG is typically completely destroyed, atrophy is gradual and progressive in nfvPPA[20,40]. Since functional and structural changes in neurodegenerative disease do not necessarily correspond directly, this raises the question of to what extent surviving neural tissue is functional. In a recent study, Wilson et al showed that the left posterior IFG is no longer differentially recruited for the processing of syntactically complex sentences in nfvPPA, so this region is not only structurally abnormal, but is also functionally compromised[36].

Semantic Memory

Semantic Memory refers to our mental representation of the meaning of words, objects, people and other concept-based knowledge unrelated to specific experiences and independent of context and personal relevance[41]. Semantic memory includes conceptual knowledge that does not involve memory of a specific event and is usually shared by individuals of the same cultural background. Conceptual knowledge can be assessed with a variety of tasks including picture naming; word, picture, sound or color matching; object/non-object decision; feature generation and semantic association. Such tasks assess different components of semantic memory (e.g. knowledge of perceptual features or semantic associations), across a range of modalities (e.g. visual, auditory or tactile) and material types (e.g. verbal or non-verbal)[42-45]. An example of a semantic association test is the word and picture versions of the Pyramids and Palm Trees test[46,47]. This test is widely used for the clinical assessment of semantic memory in neurodegenerative disease. The subject is shown a triad of stimuli (either words or pictures) – a reference (eg. pyramid) and two choices (eg. palm tree or pine tree). The subject is then asked to identify which of the two choices is most closely associated with the reference stimulus.

The anatomical basis of semantic memory is a topic of active debate within the neurological and neuroscience community[47-49]. Specific disorders of semantic memory have only

recently been introduced as a concept in neurology textbooks and are still often confused with receptive aphasia. However, in aphasia a comprehension deficit is limited to words, while in a semantic memory disorder the deficit is more generalized and comprises other modalities, such as visual (pictures) and auditory (sounds) stimuli, although to a different degree[50]. One of the reasons why semantic deficits were not considered in classical behavioral neurology is that the discipline is based on the study of stroke patients. Since stroke does not often occur in the anterior temporal lobes (ATL), vascular patients rarely present with semantic memory deficits, which were easily overlooked. Instead, the most typical pathologies causing a relatively isolated semantic memory disorder are degenerative, specifically the semantic variant of primary progressive aphasia (svPPA) [42]. Alzheimer's disease also often causes semantic memory impairment but usually in the context of a more generalized memory deficit[51]. SvPPA is a neurodegenerative disorder within the spectrum of frontotemporal lobar degeneration and has recently been associated with deposition of ubiquinated TDP-43[52-54]. Macroscopically, svPPA is associated with bilateral ATL atrophy that later spreads to ventromedial frontal cortex. Although bilateral ATL is the most common presentation, cases with significant right or left asymmetrical involvement have been described. SvPPA is clinically characterized by progressive loss of meaning of words, objects and people, surface dyslexia in the context of relatively spared fluency, syntax and phonology. Later behavioral deficits often occur, comprising compulsions, loss of empathy and disinhibition. Clinically, svPPA patients often come to the clinic complaining of difficulties in finding and understanding words, but a careful examination comprising low-frequency and low-familiarity items invariably brings to light a more generalized semantic memory deficit. For instance, a typical svPPA behavior is to appear puzzled looking at the octopus and to ask the examiner "what is this?". Typical is also the deficit in recognizing famous people, not only from pictures (it is not a form of visual agnosia) but also from the proper name. Until recently, the role of the ATL in semantic memory was challenged by some because patients with left temporal lobe resections for tumor did not show a severe semantic deficit. A recent paper suggests that bilateral ATL lesions are necessary to cause the semantic impairment[55].

The initial data from svPPA supported the view that there is a single, "amodal" semantic system, because patients showed deficits in all modalities and in all categories. However, recent evidence suggest that while both ATLs are involved in semantic memory, their role might be weighted by an interaction between the modality to be processed (verbal for the left ATL; visual for the right ATL) and the type of information and operation requested (abstract and unique-level for the left ATL and emotional/socially-relevant for the right ATL)[56-60].

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