

Language capacities in dementia

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Summary

Language capacities in dementia are increasingly studied. Major advances in cognitive neuropsychology and functional neuroanatomy have shown extensive language networks in frontal, parietal and temporal cortex and their subcortical connections mainly, but not exclusively, in the left hemisphere. The main aphasias following strokes or brain tumours that correspond to the classic Wernicke-Lichtheim connectionism model are, therefore, rarely encountered. Moreover, degenerative pathology is never restricted to a focal location and often associates both motor and semantic aspects of speech and language. Primary progressive aphasias including agrammatic/non-fluent, logopenic and semantic variants served as models of relatively pure language deficits and helped our understanding of other dementias. Agrammatic/non-fluent aphasia and/or speech apraxia constitute clinical criteria for corticobasal degeneration and supranuclear palsy, and can occur in isolation before corticobasal or supranuclear syndromes emerge. In the classic form of Alzheimer's disease, word-retrieval anomia is frequent, as a result of lexico-semantic difficulties. Alterations in pragmatics are increasingly recognised. Verbal fluencies constitute the main language difficulties in subcortical vascular dementia, which is still poorly studied. In the continuum Parkinson's disease / Parkinson's disease with dementia / dementia with Lewy bodies, executive and working memory deficits at least partly explain discourse organisation difficulties and impaired sentence processing. Patients with the behavioural variant of frontotemporal dementia show verbal communication deficits secondary to pragmatic difficulties. In the near future, better phenotype-genotype correlations made using modern cognitive neuropsychological models and computerised magnetic resonance imaging (MRI), functional MRI and *in-vivo* molecular neuroimaging will improve our diagnostic accuracy of the main dementias, help better to follow up patients and benefit communication of caregivers with patients.

Key words: language; dementias

Introduction

Dementia classically impairs multiple cognitive domains, which results in a decline in social and occupational functioning. Most clinical research has been focused on the memory difficulties (and more specifically on episodic memory) that are the core clinical feature of Alzheimer's disease

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(AD), the most frequent sporadic form of dementia worldwide. Nevertheless, in the last decade, language has been increasingly recognised as a marker for distinguishing between various dementias, because of major advances in cognitive neuropsychology, aphasiology and the functional neuroanatomy of language. Apart from diagnosis, a better understanding of language in dementia is extremely important. Obviously, patients with communication difficulties and dementia are going to increase in the next decade, because of the growth of the older segment of the population. A better selection of patients who will benefit from speech therapy is required. Finally, it may help to teach caregivers since communication is crucial in the patient's care, management and interactions. After a few words on main language domains and functional neuroanatomy, we will focus on language findings in the main dementias. We will briefly summarise current data on primary progressive aphasias (PPA), which are heterogeneous diseases deriving from non-Alzheimer's and Alzheimer's pathologies, and then discuss language capacities in the main dementias, which are AD, fronto-temporal dementias (FTD), vascular dementia (VaD), and dementia with Lewy body (DLB). Language capacities in amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease (HD) and Creutzfeldt-Jakob disease (CJD) will be only briefly presented, because of clinical and neuropathological overlaps with the main dementias and/or special interest for neurologists.

Modern aphasiology and functional neuroanatomy

Language is no longer understood as the classic Wernicke-Lichtheim connectionism model (i.e. receptive aphasia, expressive aphasia and conduction aphasia resulting from disconnection in the arcuate fasciculus), but as a complex cognitive function that is widely distributed in the brain. It includes phonology (the system that deals with phonemes or sounds of language), syntax (the rules and principles of language including grammar), semantics (the meaning and relation between words) and pragmatics (the way we infer the meaning depending on the context, including emotion, inference, implicature, conversational competence, social distance etc.), as well as attention and resource capacity, phonological loop (short-term memory which stores verbal data/phonemes over brief intervals of time) and episodic buffer (the system that links working memory to episodic memory). Contemporary cognitive neuropsychology and advances in neuroanatomical tools using magnetic reso-

nance imaging (MRI) and functional MRI (fMRI) have provided a new understanding of the language network that not only encompasses classic language areas in the left hemisphere (Wernicke's area, Broca's area, arcuate fasciculus), but also their cortical and subcortical connections. The reader may refer to Price, who recently reviewed the functional neuroanatomy of language [1]. In sum, auditory processing involves bilateral superior temporal gyrus around Heschl's gyrus including the left inferior frontal cortex, temporo-parietal cortex and left planum temporale. Speech sound (or phonological) processing is mainly associated with activations in the left posterior superior temporal cortex and the left anterior superior temporal gyrus, the left inferior frontal gyrus and the ventral supramarginal gyrus. Speech comprehension (when familiar sounds are recognised and mapped onto their meaning or semantics) mainly occurs in the left anterior temporal pole, but also in the left posterior temporal areas, ventral inferior frontal and possibly the dorsal superior frontal cortex and angular gyrus. For speech production, word retrieval from semantics is associated with activations in the left middle frontal and the left middle and inferior temporal cortices, the cerebellum and the anterior insular cortex when retrieval becomes more difficult; covert articulation (processing occurring prior to overt articulation, i.e. silent) involves the ventral pars opercularis, the ventral premotor cortex and the cerebellum; overt articulation (or producing the sound of speech, i.e. speaking aloud) activates the sensorimotor cortex (which controls orofacial muscles, laryngeal activity, phonation and voluntary control of breathing), the thalamus, the supplementary motor areas (SMA), the left caudate and the left putamen. Auditory motor feedback during speech production (useful for monitoring and correcting speech errors) probably occurs in the main core language areas in the temporal lobe (superior temporal sulcus, superior temporal gyrus and planum temporale). The written word (visual processing) involves a large region in the ventral occipito-temporal cortex. Converting spelling (orthography) to sound (phonology) is complex since it involves sublexical, lexical and semantic routes; lexico-semantic reading is located in the left ventral occipito-temporal and left ventral inferior frontal gyrus; non-semantic phonological reading links the superior temporal and ventral inferior parietal to the dorsal precentral gyrus.

Language examination

Examination of patients presenting with language difficulties is beyond the scope of this review and the reader may refer to the article of Martory et al. in this issue. In brief, clinical assessment starts with the history of language difficulties. When did the symptoms start? Were they isolated or accompanied by other cognitive symptoms? Did the patient present with emotional and/or behavioral symptoms? Did the patient complain of neurological symptoms, especially dysarthria, micrographia, abnormal movements (tremor, myoclonus, ...), rigidity, dystonia, hypokinesia, loss of balance or falls? Clinical language assessment includes spontaneous speech (language competency, fluency, pauses, circumlocutions, phonological transformations), confrontation naming and designation, oral comprehension, writing, reading (written comprehension), repetition (using monosyllabic and polysyllabic words / non words as well as short and long sentences), pragmatics (prosody, metaphor comprehension, metacognition) and general meaning of discourse. Carrying out complex movements of the face on demand in order to look for orofacial apraxia is required, as well as basic motor examination of facial, lingual and laryngeal muscles for dysarthria. Both orofacial apraxia and dysarthria may accompany or mask, when severe, language difficulties. It is obviously extremely important to repeat the clinical assessment of language, as well as other cognitive and behavioural functions, over time.

Primary progressive aphasia

Primary progressive aphasia (PPAs) are heterogeneous entities that were initially described in the 80's by Mesulam, who distinguished two main subtypes (non-fluent and fluent PPA). After more than 20 years of debate and controversy, consensus diagnostic criteria for the three main variants were established in 2011 [2]: the agrammatic/non-fluent, the semantic and the logopenic primary progressive aphasia (PPA-A, PPA-S and PPA-L, respectively; see table 1 for diagnostic criteria and linguistic features). Since language deficits have an impact on other cognitive functions and most neuropsychological tests depend on verbal commands,

Table 1 Clinical diagnosis of the three variants of primary progressive aphasia (adapted from [2]).

Clinical diagnosis of PPA-A	1. Deficit in comprehension of syntactically complex sentences 2. Intact single-word comprehension 3. Intact object knowledge	Imaging-supported PPA-A diagnostic criteria include clinical diagnosis and neuroimaging showing predominant left posterior fronto-insular atrophy on MRI or hypoperfusion/hypometabolism on SPECT/PET
Clinical diagnosis of PPA-L	1. Deficit in single-word retrieval in spontaneous speech 2. Deficit in repetition of sentences and phrases 3. At least three of the following: phonologic errors, preserved single-word comprehension and object knowledge, no agrammatism	Imaging supported PPA-L diagnostic criteria include clinical diagnosis and neuroimaging showing predominant left posterior perisylvian or parietal atrophy on MRI or hypoperfusion/hypometabolism on SPECT/PET
Clinical diagnosis of PPA-S	1. Deficit in comprehension naming 2. Deficit in single-word comprehension 3. At least three of the following: deficit in object knowledge, surface dyslexia or dysgraphia, intact repetition, intact speech production	Imaging supported PPA-S diagnostic criteria include clinical diagnosis and neuroimaging showing anterior temporal lobe atrophy on MRI or hypoperfusion/hypometabolism on SPECT/PET

PET = positron emission tomography; PPA = primary progressive aphasia; PPA-A = agrammatic/non-fluent PPA; PPA-L = logopenic PPA; PPA-S = semantic PPA; SPECT = single-photon emission computed tomography

the PPAs are often misdiagnosed as dementia: verbal memory tests depend on language capacities and detect deficits in two cognitive domains, therefore fulfilling the criteria for a dementia diagnosis although patients have normal or near-normal daily activities. In advanced stages, aphasia is global with severe loss of fluency or mutism, and intense or complete comprehension deficits. When output is preserved, it is

restricted to single words, palilalic syllables or meaningless logorrhoea (phonemic jargon). Neurological signs and behavioral symptoms frequently appear. PPA cases must be followed up over time because corticobasal or supranuclear palsy syndromes (CBS and SPS, respectively) and/or behavioural symptoms may appear during the course of the disease [3] and orient the diagnosis. Language features are now part of the clinical phenotypes of most common tau neuropathologies such as corticobasal degeneration (CBD) [4] and supranuclear palsy (SP) [5], usually agrammatic/non-fluent aphasia or speech apraxia or their combination (tables 2 and 3).

Table 2 Clinical syndromes associated with corticobasal degeneration neuropathology (adapted from [4]).

1.	Probable CBS	Asymmetric presentation of at least two of the following: a) limb rigidity or akinesia b) limb dystonia c) limb myoclonus plus one of: d) orobuccal or limb apraxia e) cortical sensory deficit f) alien limb phenomena
2.	Possible CBS	One of (may be symmetric) of the following: a) limb rigidity or akinesia b) limb dystonia c) limb myoclonus plus two of: d) orobuccal or limb apraxia e) cortical sensory deficit f) alien limb phenomena
3.	Frontal-behavioural syndrome	Two of the following: a) executive dysfunction b) behavioural or personality change c) visuospatial deficits
4.	Agrammatic/non-fluent variant of PPA	Effortful, agrammatic speech plus at least one of the following: a) deficit in grammar/sentence comprehension with relatively preserved single word comprehension b) groping, distorted speech production (apraxia of speech)
5.	Progressive SP syndrome	Three of the following: a) axial or symmetric limb rigidity or akinesia b) postural instability or falls c) urinary incontinence d) behavioural changes e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

CBS = corticobasal degeneration; PPA = primary progressive aphasia; SP = supranuclear palsy

Bold text indicates the language variant.

Table 3 Clinical syndromes associated with supranuclear palsy neuropathology (adapted from [5]).

1.	Typical progressive SP: postural instability, axial more than limb rigidity and common cervical dystonia, vertical gaze paresis, frequent depression, apathy, bradyphrenia
2.	Progressive SP with frontal lobe dementia: cognitive impairment (with slowing of mental processes and memory deficits with retrieval difficulties) and personality changes often with abulia and apathy and less often disinhibition (similar to frontal variant-FTD)
3.	Progressive SP with corticobasal syndrome: asymmetrical rigidity, ideomotor apraxia, myoclonus, dystonia, cortical sensory loss and alien limb phenomenon
4.	Progressive SP with primary lateral sclerosis: primary lateral sclerosis (pyramidal signs, hyperreflexia, spasticity and clonus)
5.	Progressive SP with progressive non-fluent, agrammatic aphasia or apraxia of speech
6.	Progressive SP with asymmetry, tremor, extra-axial dystonia and levodopa response
7.	Progressive SP with pure akinesia and gait failure

FTD = frontotemporal dementia; SP = supranuclear palsy

Bold text indicates the language variant.

Alzheimer's disease

AD neuropathology (beta amyloid and tau lesions) might be the most common pathology underlying PPA-L, and the majority of patients with this subtype of aphasia progress to full clinical AD over time [2]. Patients with the classic sporadic form of AD often present at an early stage with word-retrieval anomia, literal and neologistic errors, reduction in phrase length, difficulties in sentence repetition, and impaired comprehension, mainly of written sentences [6]. The patient then typically show deficits at the level of oral production, semantic dissociations, and both quantitative and qualitative discourse impoverishment [7]. Declines in written production and in comprehension are usually observed later in the disease, and the severity of language deficits globally parallels global cognitive impairment [8]. Language impairments in AD remain, however, heterogeneous, and their dynamics show a high degree of variability. Language deficits could manifest at the onset [9], or later in the course of the disease [10, 11]. Oral and written picture description impairs discourse because of word findings difficulties, diminished pictorial themes and informative contents, and error monitoring difficulties. Patients use more frequent pauses and hesitations [12], "ohs" and "ums" and longer formulaic phrases [13], or increased use of self-referential tags, or checks of the certainty of the question [14]. Some authors favour impairment at the lexico-semantic (or microlinguistic) level [15] and others at the macro-linguistic supra-sentential one (i.e. thematic coherence) [16]. Rousseaux et al. found word comprehension difficulties, and to a lesser extent paraphasias suggesting lexico-semantic difficulties and moderate impairment in pragmatics (response to open questions and presentation of new information); speech outflow, speech articulation and syntax and non-verbal communication were grossly intact [17], but their sample did not include advanced stages of the disease. In the early stage of autopsy-confirmed AD, semantic processing (i.e. semantic units of discourse samples) was altered, particularly for actions and subjects rather than for locations and objects [18]. Pragmatics, assessed with a referential communication task (trial repetition in order to achieve common references), was not intact in a small sample of AD patients, as compared with healthy controls: although AD patients benefited from the task repetition, they were significantly worse at integrating previous shared information and referential expressions [19]. This alteration was not associated with

executive deficits. Interestingly, the percentage of conversational gestures was globally reduced, suggesting parallelism between speech and gesture degradation [20].

Dementia with Lewy bodies

Both Parkinson's disease (PD), Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) belong to a family of degenerative diseases secondary to alpha-synuclein inclusions named Lewy bodies in the substantia nigra, the cortex and the brain stem. PD patients do not have prominent cognitive deficits, unlike PDD and DLB, which broadly share similar executive, visuospatial and memory difficulties.

In PD, language difficulties have been reported only recently (for a review see [21]). PD patients are less accurate in the processing of long complex sentences, which is probably secondary to impaired verbal working memory, executive resources, sequencing abilities, semantic priming and set switching. PD patients also show verb generation and metaphoric understanding difficulties.

Aphasia is not a core cognitive feature of DLB, but language capacities are not entirely normal. When 16 DLB patients were compared with 16 AD patients matched for age and level of dementia, confrontation naming, letter and category fluencies, repetition, and oral and written comprehension showed a similar degree of impairment [22]. More recently, DLB patients were described who had script comprehension difficulties (loss of accuracy in ordering judgment and significantly slower) when compared with normal controls and patients with PD, which were correlated with executive deficits and frontal atrophy [23]. The same group found sentence processing difficulties related to working memory deficits and impairment of speech fluency that both correlated with the measure of brain atrophy [24]. Executive impairments probably also explained organisation difficulties of narrative discourse in non-aphasic DLB patients [25]. Since the most common form of DLB is not the pure Lewy body form but the mixed variant (including both Alzheimer's and Lewy body pathologies), cases of PPA followed by hallucinations, delusions and Parkinsonism have been described [26, 27]. In the first case, Alzheimer's pathology in the left temporoparietal cortex was found. In the second, although AD cerebrospinal fluid biomarkers were negative, language anomalies (corresponding to the logopenic variant, see above) strongly suggested AD neuropathology.

Vascular dementia

Strokes and/or small-vessel disease (diffuse leucoaraiosis) both lead to vascular cognitive impairment and dementia (VaD). Strategic strokes resulting in dementia and aphasia are mainly located in the left central paramedian nucleus of the thalamus, disrupting frontal-basal ganglia-thalamus loops [28]. In patients matched for severity of dementia, multi-infarct dementia patients were more impaired in word recognition, naming and repetition than AD patients who had more difficulties understanding grammatical structures

[29]. Subcortical small-vessel disease or diffuse leucoaraiosis is a frequent finding, commonly leading to executive dysfunction of various severities. Clear-cut neuroanatomical correlations with clinical findings are often equivocal and largely unresolved since co-existent neurodegenerative pathology may occur. In mild to severe dementia patients, repetition difficulties were more impaired in AD than VaD [30]. When patients within the AD/VaD spectrum, very early dementia and with various degree of leucoaraiosis that were correlated to neuropsychological functions, no leucoaraiosis threshold was found for the language measures (verbal fluency), unlike working memory and executive functions [31].

Frontotemporal dementia

Frontotemporal syndromes include the language variants (PPA-A, PPA-S, see above) and the behavioural variant (bv-FTD) that belong to tauopathies or TDP-43 proteinopathies. In the latter, language deficits contribute to the differential diagnosis from AD. In longitudinal follow-up bv-FTD patients showed a faster decline than AD patients and shared several linguistic overlaps with PPA, suggesting they belong to the same spectrum of disorders [32]. Bv-FTD patients have decreased speech output and conversational initiation, echolalia, word finding difficulties and semantic paraphasias [33], verbal stereotypia (such as ah, ah, ah), sentence comprehension deficits in relation to syntactic complexity and discourse difficulties (fewer accurate events and more incomplete events, diminished global and local connectedness, difficulties in maintaining the theme of the story) [34]. Unexpectedly, patients with bv-FTD were severely more impaired than matched AD patients in personal communication (greeting, attention, communication) and verbal communication, because of pragmatic problems [17].

Motoneurone disease

Amyotrophic lateral sclerosis (ALS) belongs to a spectrum ranging from pure ALS to ALS with dementia and more specifically FTD (FTD-ALS), because of common molecular neuropathology (TDP-43 proteinopathy) and neurogenetics. In ALS patients without dementia compared with age-matched controls using a brief cognitive and behavioural battery, language difficulties were even more prevalent (35%) – and more specifically impaired spelling – than executive deficits (23%) [35]. Another group replicated this finding, with mild impairment of language in non-demented FTD patients occurring in 43% of their sample, compared with 31% of patients with executive deficits [36]. Language deficits did not correlate with bulbar-onset disease. More interestingly, both language and executive deficits shared only 44% of variance in terms of performance, suggesting dissociable phenotypes. In this sample, category fluency and semantic associations were not significantly different from normal controls. Hexanucleotide repeat expansions in the C9orf72 gene being a major cause of both ALS and FTD, when C9orf72 positive ALS patients were compared with

C9orf72 negative ones, apathy, disinhibition and loss of empathy were significantly more prevalent in the first group, but no differences were found in terms of language and cognitive impairment [37].

Huntington's Disease

Language capacities are not classically altered in early Huntington's disease (HD) patients. In genetically confirmed HD, verbal fluency, oral comprehension, repetition, oral agility, reading comprehension and narrative writing were impaired [38]. Various motor speech difficulties have been described, such as deviations in phonation (increased pitch, harsh voice), reduced coordination of tongue and lips, impaired speech timing and abnormal prosody, verbal stereotypia, which usually worsen in parallel with disease severity [39]. In gene-positive presymptomatic individuals, speech rate significantly differed from controls [40]. They were slower to produce words and left longer silences between and within words. Syntactic difficulties not due to working memory impairment were attributed to striatum damage [41].

Creutzfeldt-Jakob disease

In Creutzfeldt-Jakob disease (CJD), various poorly described aphasia subtypes or linguistic deficits may occur, rarely in isolation and mimicking neurodegenerative PPA [42]. More recently, PPA-A with speech apraxia [43] and PPA-L [44] have been described. These rare cases underlie the importance of diffusion weighted imaging-sequence MRI in any patient presenting with subacute or atypical language difficulties.

Conclusion

Neurodegenerative diseases are heterogeneous conditions that disrupt neuroanatomical language networks at different levels and, therefore, overpass classic aphasia syndrome. Language is increasingly recognised as a clinical marker of neurodegenerative diseases (not only in AD but also in CBD, SP and DLB). Nevertheless, although clinical phenotypes may be related to distinct neuropathological processes, most phenotypes are not specific and many clinical overlaps exist between different neuropathological entities [45]. Structural and molecular neuroimaging as well as CSF markers pinpointing the neuromolecular pathology correlated with more quantified language analysis will probably allow a better understand language deficits *in vivo* in the future, and improve rehabilitation techniques and communication with caregivers.

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