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## Language impairment in neurodegenerative diseases

Language and speech are among of the most complex activities, involving cognitive-linguistic processes, motor speech planning, programming control and neuromuscular execution. Two specific brain areas generate speech: -frontal Broca's area related to speech production and articulation, and -temporal Wernicke's area responsible for speech comprehension. However, organization of language and comprehension/production of speech are mediated by broader neural network covering several cortical-subcortical regions and their connections. Some disorders of nervous system show up with language/speech changes. Language in neurodegenerative diseases may represent a specific marker to distinguish language isolated syndromes, as primary progressive aphasia (PPA) and its variants, but also to diagnose neurodegenerative disorders characterized by language impairment within other cognitive and neurological disorders, as Parkinson, Alzheimer, Amyotrophic Lateral Sclerosis, Multiple Sclerosis. The study of language network may contribute to greater understanding of extension of neurodegenerative processes. Our article is a review on language impairments that characterize the most frequent neurodegenerative diseases.

*Keywords:* language, speech, neurodegenerative diseases, cognitive functions.

### 1. Introduction

“Language” and “speech” are among the most complex human activities involving cognitive-linguistic processes, speech motor planning, programming check, and neuromuscular execution.

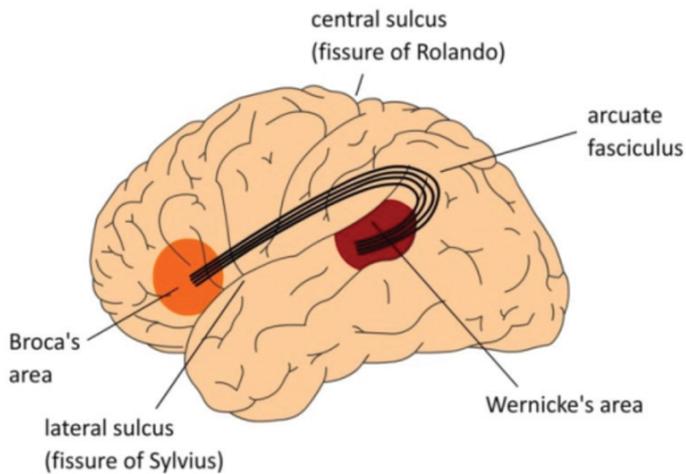
“**Language**” is the cognitive ability to communicate, to assign or decode symbols and to organize or decipher sentences and phrases. In this definition, language is the “*engine*” of communication. When language is impaired due to injury to the brain, the disorder is referred to “*aphasia*”.

“**Speech**” is a motor ability of speaking, involving the lungs, trachea, respiratory muscles, vocal cords, mouth, tongue and velum, facial muscles and is defined as the mechanism by which language is expressed and articulated orally. Some individuals may have a motor speech deficit, making it difficult to produce words, e.g. “*dysarthria*”, or to coordinate complex movements for articulation, e.g. “*speech apraxia*”.

In 1874, Carl Wernicke proposed the first brain behavioral model, named Wernicke-Geschwind model, based on the idea that language consists of two basic functions: *a*) language comprehension which is a sensory/perceptual function, and *b*) language production, which is a motor function. In this simple model, the language function was localized in two main regions: (1) an area sited in the *left* temporal lobe (known as *Wernicke's area*) that contains auditory images of words

responsible for speech perception. A lesion at this level causes “*sensory or fluent aphasia*”; (2) an area located in the *left* inferior frontal lobe (known as *Broca’s area*) that contains the motor memories responsible for speech production. A lesion at this level causes “*motor aphasia or nonfluent aphasia*”. These two regions communicate with each other through a bundle of fibers, identified as the *arcuate fasciculus*, essential for language, from spontaneous speech and word retrieval to repetition and comprehension skills. Lesion of the arcuate fasciculus can result in *conduction aphasia* as the inability to repeat words or phrases (Figure 1).

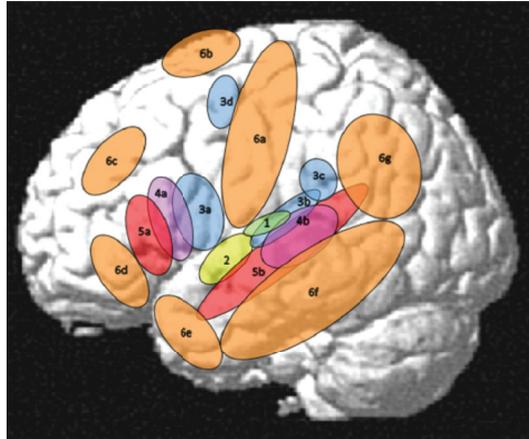
Figure 1 - *Wernicke-Geschwind model* (from Hagoort P. 2013, n. 22)



However, this simple model is obsolete, and it is known that language involves several distinct but integrated areas located in a vast network of many brain regions. These brain regions are represented by a “core” and a number of “margin regions” (Hertrich, Dietrich & Ackermann, 2020).

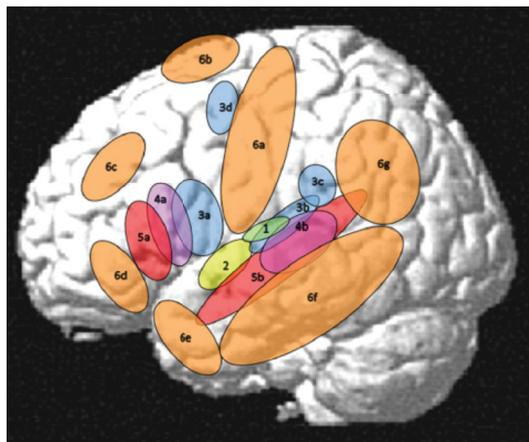
The “**core**” language network is restricted to extensive areas of the *left* temporal and frontal lobes including: 1) the auditory cortex as the primary input structure; 2) the auditory area of word form as the central region of comprehension of the words, – “Wernicke’s area”; 3) the posterior part of the frontal language area, – “Broca area” and the posterior superior temporal gyrus as phonological regions that link an auditory phonetic to an articulatory linguistic code; 4) the middle part of the frontal language areas and the superior and middle temporal gyrus as for syntax processing, manipulation and detection of structures above the word level; 5) the anterior part of the frontal language areas, anterior and posterior parts of superior temporal gyrus as fundamental lexical-semantic areas linking phonological codes to lexical meanings (Hertrich *et al.* 2020) (Figure 2a).

Figure 2a - Core language network. (1) Auditory cortex; (2) Auditory area of word form as the central region of comprehension of the words; (3 a,b,c,d) Phonological areas linking an auditory-phonetic to an articulatory language code; (4 a,b,) Syntax processing, manipulating and detecting structures above word level; (5a,b) Lexical-semantic core areas linking phonological codes to lexical meanings (from Hertrich et al. 2020, *Front Commun*, n.23)



The “margin regions” are other **bilateral** brain structures and networks that complete the basic linguistic system, represented by 1) parietal and posterior temporal regions contributing to sensorimotor processing, 2) inferior temporal-occipital regions predominantly linked to visual object representations and their association with language processing, and 3) the temporal pole as a language interface toward the processing of emotions, valence, and social cognition (Hertrich et al. 2020) (Figure 2b).

Figure 2b - Margin language network. Margin regions: (6a) Sensorimotor cortex; (6b) Supplementary motor area (SMA) and pre-SMA; (6c) dorsolateral prefrontal cortex; (6d) orbitofrontal cortex; (6e) temporal pole; (6f) middle and inferior temporal regions; (6g) parietal and temporoparietal regions (from Hertrich et al. 2020, *Front Commun*, n.23)



Finally, subcortical structures are also involved in the production of language, as the thalamus, caudate nucleus, globus pallidus, subthalamic nucleus, substantia nigra and cerebellum, which on the one hand regulate and coordinate the motor aspects of language, on the other hand play a role in the processing of language-cognitive functions.

Specifically, the cerebellum exerts control over speech and language functions in several ways. The most obvious is the regulatory motor control, which is a major function of the cerebellum, *-ataxic dysarthria* resulting from injury. In addition, several neuroanatomic, clinical, neurophysiological and neuroimaging evidences demonstrated the crucial role of the cerebellum in cognitive processing and language function. Functional MRI studies have shown that cerebellum has reciprocal connections with both left inferior frontal gyrus and left lateral temporal cortex (Booth, Wood, Lu, Houk & Bitan, 2007), as well as associations between neural activity in the posterolateral cerebellar and cortical activity of regions related to social cognition, memory, language and executive functions (Highnam, Bleile, 2011). Scientific literature defines this concept as “*cerebellar neurocognition*” (Baillieux, De Smet, Paquier, DeDeyn & Marien, 2008).

Similarly, the basal ganglia and the connected thalamus may control speech and language in several ways. The basal ganglia have a function in motor processing, including articulation, but they are also involved in the cognitive control required by linguistic and non-linguistic processing (Nadeau, 2021; Booth *et al.*, 2007).

The thalamus moderates the transfer of lexical information to cortical areas. Indeed, a thalamic lesion can lead to a loss of spontaneous speech due to the interruption of the excitatory input from the thalamus to the cortex. (Nadeau, Crosson B, 1997)

Neurodegenerative diseases are a large group of disorders affecting the nervous system and represent a major common cause of disability worldwide. One of the most difficult challenges for individuals with neurodegenerative disease is the insidious onset of communication impairments.

Our article is a review on language impairments that characterize the most frequent neurodegenerative diseases.

## 2. *Neurodegenerative diseases and language impairments*

Neurodegenerative diseases are a heterogeneous group of disorders characterized by the progressive degeneration of the structures and functions of the central nervous system. Several factors contribute to neurodegenerative diseases, including genetic mutations, neuroinflammation, mitochondrial dysfunction, neuronal cell death, misfolded protein aggregation, i.e. amyloid- $\beta$  ( $A\beta$ ) and tau in Alzheimer’s Disease, mutant huntingtin (mHTT) in Huntington’s chorea,  $\alpha$ -synuclein in Parkinson’s Disease, and TAR DNA-binding protein-43 (TDP-43), fused in sarcoma/translocated in liposarcoma (FUS/TLS) in Amyotrophic lateral sclerosis, (Hou, Dan, Babbar, Wei, Hasselbalch, Croteau & Bohr, 2019; Peng, Trojanowski & Lee, 2020).

Neurodegenerative diseases share some pathological and clinical signs related to the atrophy of the brain area connected to specific functions, such as cognitive functions with memory loss, disorientation, language impairment.

The impairment of language or speech functions occurring in neurodegenerative diseases could be attributed to disruptions in linguistic processes (i.e., related to conceptualization, word-finding, syntax, semantics, and/or phonology), or to motor processes involved in the planning and programming (i.e., apraxia of speech) or executing speech motor commands (i.e., dysarthria), or any combination of these processes. Language deficits are present in several neurodegenerative diseases, sometimes in the early stages, as a selective and prominent symptom, as in Primary Progressive Aphasia (PPA), or in combination with other cognitive and neurological disorders, as in Alzheimer's disease (AD), or movements disorders.

Our article is a review on the most important and common neurodegenerative diseases as Parkinson's disease (PD), Alzheimer's disease (AD), Frontotemporal dementia (FTD), Amyotrophic Lateral Sclerosis (ALS), and multiple sclerosis, all showing complex and heterogeneous impairment of language functions.

## 2.1 Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by the progressive loss of dopaminergic neurons, mainly in the pars compacta of substantia nigra (Damier, Hirsch, Agid & Graybiel, 1999; Redgrave, Rodriguez, Smith, Rodriguez-Oroz, Lehericy, Bergman & Obeso, 2010). Furthermore, there is some evidence that caudal, brainstem and other non-dopaminergic neurons are also affected. Speech and language impairments have been described in approximately 90 % of patients with PD. In particular, the impairment of motor function in PD may involve also the motor speech control, with difficulty in breathing, phonation, articulation, resonance and prosody (Goberman, Coelho, 2002). Patients with PD may have low volume (hypophonia), impaired voice quality (dysphonia), reduced range of articulatory movements (hypokinetic) and reduced pitch/volume inflection to convey meaning or emotion (hypoprosodia). *"Hypokinetic dysarthria is the generic term for this set of defects"*. Hypokinetic dysarthria worsens with disease progression, is closely related to overall intelligibility, and becomes very unresponsive to pharmacological treatments. The haste (words rushing together quickly) and disfluency (from hesitation to loss of pace), the tendency to accelerate emission of sounds, the overlapping syllables and omitting the end of words may further impair understanding. Echolalia and palilalia may characterize the language features in more advanced stages of the disease, and the degree of communication impairment can progress to inaudible and unintelligible speech. In addition to the above-described language impairment, patients with PD may have subtle deficits in processing and comprehension of verbal and non-verbal emotional aspects of communication related to cognitive-linguistic dysfunction (Grossman, Crino, Reivich, Stern & Hurtig, 1992; Grossman, Kalmanson, Bernhardt, Morris, Stern & Hurtig, 2000).

## 2.2 Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease that affects millions of people worldwide and is mostly recognizable through its primarily cognitive syndrome: the dementia. It is a progressive neurological disease that results in irreversible loss of neurons, in particular in the cortex and hippocampus, which leads to characteristic memory loss and behavioral changes (McKhann, Drachman, Folstein, Katzman, Price & Stadlan, 1984).

AD is characterized by aberrant accumulation of beta-amyloid plaques and tau protein tangles with consequent disruption in brain networks. A recent study reported a relationship between beta-amyloid deposition and brain regions involved in memory, visual-spatial, and language functions (Baboo, Prasad, Mahajan & Baths, 2022).

AD dementia is associated with heterogeneous and broad cognitive impairment; the most typical hallmarks are impairment of memory, executive function, and language (Vigo, Coelho & Reis, 2022). In AD, language and memory functions are closely related and difficulties in productive language, speech understanding, and memory impairment overlap.

Language impairments have been reported to occur in preclinical AD, as well as in mild, moderate, and severe AD dementia (Bayles, Tomoeda, Cruz & Mahendra, 2000). In the early stage of AD, many communication skills remain intact, including speech sound production, grammar, and conversational abilities; the patients may show deficits in word finding, comprehending complex conversation and memory lapses. In the middle stage, several deficits are found in word finding, understanding of complex tasks, reading comprehension, and impairment in many domains of memory. The linguistic deficit mainly occurs with a decline in lexical semantic abilities, word comprehension and impaired verbal fluency. (Forbes-McKay, Venneri, 2005; Taler, Phillips, 2008; Catricalà, Della Rosa, Plebani, Perani, Garrard & Cappa, 2015). In the late stage, patients show very limited expressive language, inappropriate word choice, echolalia and verbal stereotypies (Ferris, Farlow, 2013), up to mutism, severe deficits in auditory comprehension and memory deficits in all domains.

## 2.3 Frontotemporal dementia (FTD)

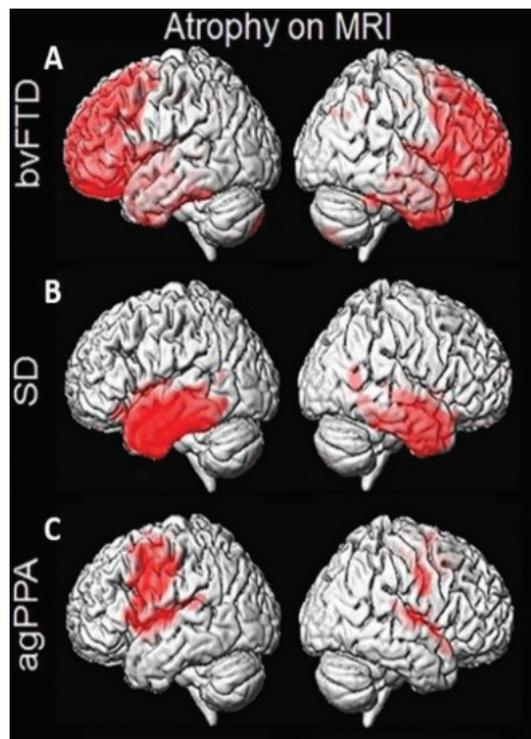
Frontotemporal dementia (FTD) is a group of clinically, pathologically and genetically heterogeneous disorders that primarily affect the left frontal and temporal lobes of the brain. The FTD is clinically characterized by progressive impairment of executive functions, changes in behavior, and a decrease in language proficiency (Bang, Spina & Miller, 2015). The most common genetic causes are mutations in progranulin, or the microtubule-associated protein tau, or a hexanucleotide repeat expansion in C9ORF72. Clinical phenotypes vary across the different genetic mutations.

The FTD is classified into four distinct core clinical syndromes, including behavioral-variant FTD (bvFTD) and three varieties of primary progressive aphasia (PPA), a) the nonfluent/agrammatic-variant primary progressive aphasia (nfvPPA),

b) the semantic-variant primary progressive aphasia (svPPA), and c) the logopenic variant PPA (lv-PPA):

- The *Behavioral variant frontotemporal dementia* (bvFTD) is the most common frontotemporal disorder that involves changes in personality, behavior and judgment, up to in awkward social situations. Patients are often unaware of their inappropriate behaviors (Rascovsky, Hodges, Knopman, Mendez, Kramer, Neuhaus, van Swieten, Seelaar, Dopper, Onyike, Hillis, Josephs, Boeve, Kertesz, Seeley, Rankin, Johnson, Gorno-Tempini, Rosen, ... & Miller, 2011). Over time, also speech and/or motor problems may occur. Studies of structural imaging show atrophy in frontal regions (orbitofrontal, middle frontal gyrus, rostromedial prefrontal cortex, pre-supplementary motor cortex), insula (dorsal and ventral anterior insula extending to posterior insula at late stages), anterior/mid cingulate cortex, anterior temporal lobes and subcortical structures (basal ganglia, thalamus, hippocampus), as well as cerebellum (Whitwell, 2019) (Figure 3-A).

Figure 3 - Pattern of atrophy in FTD clinical phenotypes. **A** in bvFTD: atrophy in frontal, insula, anterior/middle cingulate cortex, anterior temporal lobes and subcortical structures: basal ganglia, thalamus, hippocampus, and cerebellum; **B** in svPPA: atrophy in anterior temporal pole (left>right hemisphere), frontoinsula, left middle and inferior temporal gyri, fusiform gyri, amygdala; **C** in lvPPA: atrophy in inferior frontal gyrus, dorsolateral prefrontal cortex, supramarginal gyrus and the parietal lobes (Image adapted from Whitwell J.L. 2019, *Prog Mol Biol Transl Sci.*, n.51)



- The *Primary progressive aphasia (PPA)* involves changes in the ability to communicate, use language to speak, read, write, and understand what others are saying. Problems with memory, reasoning, and judgment as well as behavioral changes may develop with disease progression (Gorno-Tempini, Hillis, Weintraub, Kertesz, Mendez, Cappa, Ogar, Rohrer, Black, Boeve, Manes, Dronkers, Vandenberghe, Rascovsky, Patterson, Miller, Knopman, Hodges, Mesulam & Grossman, 2011) As above reported, the PPA includes three varieties according to the type of language problems encountered:
  - a. Semantic variant PPA (svPPA) (previously known as semantic dementia) is characterized by loss of ability to understand single words, or the meaning of words, or difficulty naming objects. Brain atrophy in svPPA has been reported in the anterior temporal pole (left > right hemisphere), frontoinsula, left middle and inferior temporal gyri, fusiform gyrus, amygdala and basal forebrain (Figure 3-B) (Whitwell, 2019);
  - b. Agrammatic PPA (previously known as progressive non-fluent aphasia) (nfvPPA) is characterized by errors and distortions in the sound of speech and/or agrammatism in speech (speech apraxia). In nfvPPA, greater progressive atrophy is found in inferior frontal gyrus, dorsolateral prefrontal cortex, supramarginal gyrus of the left hemisphere and the parietal lobes (Figure 3-C) (Whitwell, 2019);
  - c. Logopenic PPA is characterized by difficulty to find the right words, pauses in speech, difficulty to repeat phrases or sentences. In logopenic PPA, atrophy of left temporoparietal and posterior cingulate is found.

#### 2.4 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by diffuse upper and lower motor neuron degeneration in four districts of nervous system: bulbar, cervical, thoracic, and lumbosacral, and consequent impairment of all motor functions also including respiratory, phonatory, swallowing functions (Mitchell, Borasio, 2007).

Approximately 80 to 96 % of people with ALS will become unable to speech during the disease progression (Kuhnlein, Gdynia, Sperfeld, Lindner-Pfleghar, Ludolph, Prosielgel & Riecke, 2008).

Due to motor dysfunction, ALS patients may have a progressive mixed flaccid-spastic dysarthria that is characterized by impaired articulation, slowed speech, difficulty in producing sentences, inappropriate pauses, hypernasality, hypophonia, rough or breathy voice quality, fatigue or shortness of breath with speech, reduced utterance length due to impaired breath support, strangled voice (Kuhnlein *et al.*, 2008). The voice impairment is one of the most important aspects of the bulbar dysfunction.

However, ALS is a multi-system disorder, impacting not only motor functions but also cognitive aspects, ranging from mild impairment, in ~50 % of ALS patients, to frontotemporal dementia in ~15 % of patients (Goldstein, Abrahams,

2013; Lomen-Hoerth, Murphy, Langmore, Kramer, Olney & Miller, 2003; Neary, Snowden & Mann, 2000; Celsis, Argall, Henderson, McCombe & Robinson, 2020), with language involved up to semantic dementia or PPA (Taylor, Brown, Tsermentseli, Al-Chalabi, Shaw, Ellis, Leigh & Goldstein, 2013; Ringholz, Appel, Bradshaw, Cooke, Mosnik & Schulz, 2005; Strong, Abrahams, Goldstein, Woolley, McLaughlin, Snowden, Mioshi, Roberts-South, Benatar, HortobáGyi, Rosenfeld, Silani, Ince & Turner, 2017).

Cognitive changes in ALS generally involve executive dysfunction; however, there is evidence that language impairments are common and can occur without executive dysfunction or dementia (Rakowicz, Hodges, 1998). A very recent study reports that in non-demented ALS patients, language impairment occurs in ~23 % of cases, and may be not associated with other motor or non-motor features (Solca, Aiello, Torre, Carelli, Ferrucci, Verde, Ticozzi, Silani, Monti & Poletti, 2023).

The language impairment as extramotor feature of ALS may be present also at early stages and reflect distinct aspects of language processing, specifically in the domains of word naming, syntactic/grammatical processing, and orthographic lexical processing (Pinto-Grau, Donohoe, O'Connor, Murphy, Costello, Heverin, Vajda, Hardiman & Pender, 2021). Syntactic processing impairments are detected in the form of a reduced number of utterances, with shorter sentences (Tsermentseli, Leigh, Taylor, Radunovic, Catani & Goldstein, 2016).

Furthermore, ALS patients show difficulties in connecting one event to the next (local coherence) and in maintaining the topic of the discourse (Ash, Menaged, Olm, McMillan, Boller, Irwin, McCluskey, Elman & Grossman, 2014). Recent evidence from MRI studies confirms that the central nervous system involvement in ALS extends beyond motor areas. Whole brain volume loss and regional frontotemporal atrophy has been reported in ALS patients (Mezzapesa, Ceccarelli, Dicuonzo, Carella, De Caro, Lopez, Samarelli, Livrea & Simone, 2007; Agosta, Chiò, Cosottini, De Stefano & Falini, 2010) (Figura 4). Further, a correlation between extended gray matter involvement, beyond motor areas, and clinical features has been found (Bede, Bokde, Elamin, Byrne, McLaughlin, Jordan, Hampel, Gallagher, Lynch, Fagan, Pender & Hardiman, 2013; Mezzapesa, D'Errico, Tortelli, Distaso, Cortese, Tursi, Federico, Zoccolella, Logroscino, Dicuonzo & Simone, 2013) (Figure 5). This evidence confirms the strict relationships between extramotor gray matter impairment and cognitive deficit, also including verbal fluency and language deficits, along the ALS-FTD spectrum (Omer, Finegan, Hutchinson, Doherty, Vajda, McLaughlin, Pender, Hardiman & Bede, 2017).

Figure 4 - Regional cortical Gray matter atrophy in ALS. The main regions with lower GM volume were left middle temporal gyrus and the subgyral region (A), right inferior frontal gyrus (B), and frontal and temporal areas (C). (Mezzapesa et al, *AJNR*, 2017 n.30)

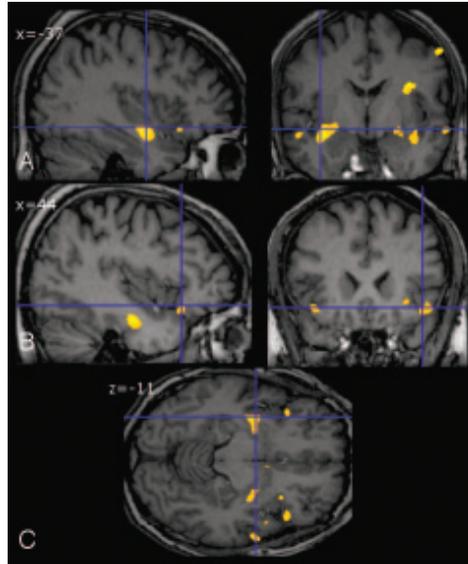
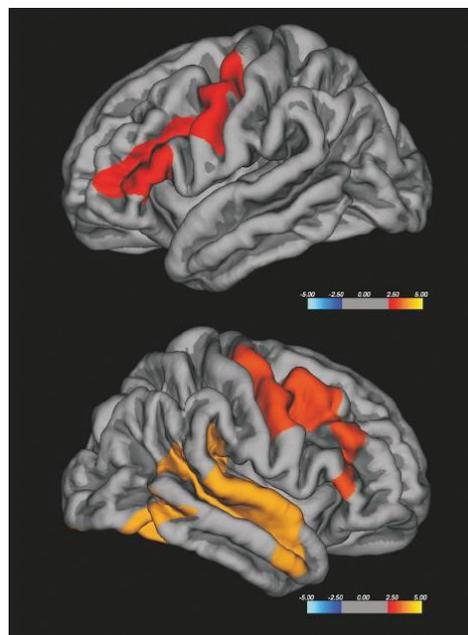


Figure 5 - Vertex-wise analysis of Cortical Thickness in ALS patients related to healthy controls. Cortical thinning in bilateral precentralcortex, bilateral middle frontal gyrus, right superior temporal and right occipital cortex. The colour bar scale represents  $t$  values. (Mezzapesa et al, *PlosOne*, 2013, n. 31)



## 2.5 Multiple Sclerosis

According to the literature, about 40-65 % of the patients with Multiple Sclerosis (MS) develop cognitive deficits, regardless of the duration and severity of the disease (DeLuca, Chiaravalloti & Sandroff, 2020; Benedict, Amato, DeLuca & Geurts, 2020).

Cortical and subcortical brain structures, including the thalamus and cerebellum, play a role in language processing, and the impairment of these regions in MS patients may result in communication disorder. Frequently patients show speech-perceived disorders and dysarthria (Murdoch, Theodoros, 2000). Some patients may have a specific type of aphasia (Demirkiran, Ozeren, Sönmezler & Bozdemir, 2006; Lacour, De Seze, Revenco, Lebrun, Masmoudi, Vidry, Rumbach, Chatel, Verier & Vermersch, 2004). Generally, the language deficits may be of various types, affecting different abilities (verbal fluency, lexical access, language comprehension, etc.) and often associated with other general cognitive deficits such as executive dysfunctions. The most commonly identified symptom is impaired word retrieval in verbal fluency (phonological and semantic) (Portaccio, Amato 2022).

## 3. Conclusions

The extensive group of neurodegenerative diseases share some pathological and clinical signs related to the atrophy of the brain areas connected to specific functions, such as cognitive functions with memory loss, disorientation, language impairment. During the course of neurodegenerative diseases, the insidious deterioration of motor speech, language, and cognition is very frequent, with a significant impact for patients, their caregivers as well for the medical management. In neurodegenerative diseases, language and speech may be impaired for motor dysfunctions affecting vocal respiration, phonation, articulation and prosody, but but also for cognitive-linguistic network failures. Language deficits sometimes may represent a selective and prominent symptom of a neurodegenerative disease, as in Primary Progressive Aphasia (PPA), or may be associated with other cognitive disorders, as in Alzheimer's disease (AD), or with motor-cognitive dysfunction, as in movement's disorders or amyotrophic lateral sclerosis. A great contribution both on the knowledge of neurodegenerative diseases and language networks has recently been provided by advanced MRI techniques.

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