

NEUROBIOLOGY OF THE LINGUISTIC FUNCTION: A REVIEW AND IMPLICATIONS FOR APHASIC REHABILITATION

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Нейробиология речевой функции: обзор и значение для афазической реабилитации

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Abstract

The Wernicke-Geschwind model has been considered the main reference in regard to the neural basis of language function. Indeed, this model has been systematically used to explain and interpret different aphasic disorders. However, recent findings across several neuroimaging studies challenge the suitability of this model to explain the cerebral dynamics observed after brain damage. This paper provides a comprehensive and up-to-date review of the most recent findings on language neuroscience. Thus, a consistent body of evidence obtained from the use of various

Резюме

Модель Вернике-Гешвинда считается основой нейронной модели речевой деятельности, которая в течение длительного времени применялась для объяснения и интерпретации различных афазических расстройств. Однако недавние результаты ряда исследований нейровизуализации ставят под сомнение пригодность этой модели для объяснения мозговой динамики, наблюдаемой после повреждения головного мозга. В статье представлен всесторонний и актуальный обзор новейших достижений в области нейробиологии языка. Так, совокупность последовательных данных, полученных в результате использования различных

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techniques (including fMRI, EEG, MEG, TMS, tDCS, among others) strongly indicates the existence of a dynamic brain network involved in language function that recruits distant brain regions across both hemispheres, hence revealing the obsolescence of traditional approaches for a complete understanding of language dysfunction. Despite these systematic and well-established findings, this and other language models are still considered nowadays in the educational and clinical practice, with detrimental implications for the successful characterization and rehabilitation of aphasic patients. Taking into account the dynamic reorganization of the language neural network, the use of modern brain neuro-modulatory techniques, together with the implementation of intense speech therapy, are discussed as the first option to be considered for the successful treatment of aphasia.

Keywords: language, brain localization, Broca's area, Wernicke's area, aphasia, neuroplasticity, CIAT, TMS, tDCS.

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методик (в том числе фМРТ, ЭЭГ, МЭГ, ТМС, tDCS и др.), убедительно указывает на существование динамической сети головного мозга, участвующей в реализации языковой функции, которая задействует отдаленные области мозга в обоих полушариях. Следовательно, традиционные подходы к полному пониманию языковой дисфункции можно считать устаревшими. Результаты исследований обладают систематичностью и надежностью, однако упомянутая языковая модель, наряду с другими подобными моделями, до сих пор используется в образовательной и клинической практике, что несет пагубные последствия для успешного исследования и реабилитации пациентов с афазией. Принимая во внимание динамическую реорганизацию языковой нейронной сети, использование современных методов нейромодуляции головного мозга и проведение интенсивной логотерапии обсуждаются как методы первого выбора для успешного лечения афазии.

Ключевые слова: язык, мозговая локализация функций, зона Брока, зона Вернике, афазия, нейропластичность, принуждающая индуцированная терапия афазии (CIAT), транскраниальная магнитная стимуляция (ТМС), транскраниальная стимуляция постоянным током (tDCS).

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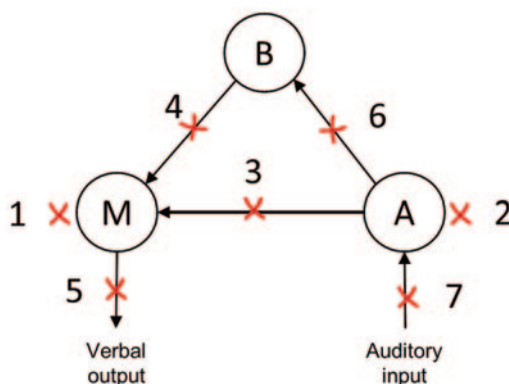
The study of cognitive functioning, and hence language processes, has not always been related to its neural substrate. With the exception of Luria's works (Luria, 1970, 1976), it was not until the decade of 70's of the past century when models in cognitive psychology started to consider the brain-behavior interplay to explain cognitive processing, likely due to methodological limitations to study the human brain function. Nowadays, however, explicative models of cognitive processing are not conceived without considering the underlying neural mechanisms, not only in relation to the responsible brain areas and their anatomical location but, importantly, in regards to its functional communication. During these years, and most likely due to the influence of historical principles such as Lashley's mass action or equipotentiality (1929), some authors have adopted rather skeptical positions regarding the usefulness of neuroimaging to localize cognitive processes, including Max Coltheart (2004), one of the founders of Cognitive Neuropsychology. Nonetheless, other more proactive proposals can be also found in the literature, such as that defined by Donald Hebb (1949), according to which the matter is not the location but the association, or what he called "*assemblies of cells*"; that is, groups of neurons distributed across different parts of the brain that are all "*turned on*" at once to contribute to the solution of a certain mental operation: "*cells that fire together, wire together*". A similar point of view has been maintained by Luria during more than 30 years when referred to the concept of "dynamic structures or constellations of brain areas" instead of neurological centers for language function (Ardila et al., 2020). Following this idea, several neuroscientists, together with computer engineers, have proposed the elaboration of the "*human connectome*" (Sporns et al., 2005), a connection matrix or map of the primary and secondary pathways that interconnect in the human brain; this is a laborious and difficult task that reunites the coordination and effort of several researchers across the world, with important implications for neurobiological research at both basic and applied levels.

Classical Perspective of Language in the Brain

In the 19th century, human language attracted the interest of different neurologists (Tremblay & Dick, 2016), who proposed an integrated model based on connections between brain areas, the "Broca-Wernicke-Lichtheim-Geschwind" Classic Model (see Figure 1). This string of names is a tribute to the main contributors to the model, which has remained without substantial modifications from its

Figure 1

Classic Model of Broca-Wernicke-Lichtheim-Geschwind



Note. Boxes represent the main centers for language processing (M = motor center or Broca's area; A = center for auditory sensory representations of words, or Wernicke's area; B = conceptual center), which communication is represented by arrows. The disruption of this network as a consequence of brain damage results in different aphasic syndromes indicated by numbers (1 = Broca's aphasia, 2 = Wernicke's aphasia, 3 = Conduction aphasia, 4 = Transcortical motor aphasia, 5 = Subcortical motor aphasia, 6 = Transcortical sensory aphasia, 7 = Pure word deafness).

proposal until the mid 20th century (Poeppel & Hickok, 2004). The model was initially proposed by Wernicke in 1874, who distinguished two different cortical areas involved in language function, located anterior and posterior to the central sulcus (Rolando's fissure) and related to motor-expressive and sensory-perceptual functions, respectively. According to the model, these two regions (traditionally named as Broca and Wernicke's areas) store motor and sensory representations for words, respectively, and participate in accessing words meaning, whose semantic representation is distributed throughout the cortex. This model predicts the symptoms for the main aphasic syndromes. Thus, if the motor area is damaged, the patient would exhibit impairment at speech production, while speech comprehension would be preserved. On the contrary, if the brain damage affects the posterior region, the reverse pattern would be expected. For these *"sensory aphasics"*, the model also predicts that, despite their fluent speech, these patients would exhibit disorganization and lack of meaning in their verbal expression, since the conceptual-sensory-motor communication network would be disrupted.

Therefore, these two cortical regions have been traditionally considered as the main brain areas involved in language function, and hence they have played a protagonist role in the vast majority of language-related studies. More recently, however, different researchers have raised concerns against the reductionism embedded in this model, as reflected in provocative titles such as *"Broca and Wernicke are dead, or moving past the classic model of language neurobiology"* (Tremblay & Dick, 2016) or *"The error of Broca: From the traditional localizationist concept to a connectome anatomy of human brain"* (Duffau, 2018). In the latter work, for instance, it

is stated that the function of Broca's area can be indeed assumed by other brain regions, since there is evidence for full recovery of language production even after complete surgical resection of this area. For this reason, an update on the functional role of these and other brain structures, their dynamics and potential reorganization after brain damage, should be considered for the better understanding of language processing in both healthy and clinical populations.

Current Anatomo-Functional Perspective of Language Function

Language is a complex cognitive function, in which several cognitive operations and interconnected brain regions are necessary in order to both understand and produce the speech (see the special issue of *Cognition* edited by Poeppel & Hickok, 2004 for a didactic exposition). Hagoort (2017) points out that the first requirement to understand the speech is to segment the spoken signal into discrete units (namely, phonemes and/or syllables), from which access their stored phonological representations. We are able to perceive and segment between 4 and 6 syllables per second; therefore, our brain can process about 3 words per second, each of them recognized in 200 or 300 milliseconds. At the same time, component morphemes, roots and affixes are also decomposed during segmentation of the word (or ensemble, during speech production) for later morphosyntactic analyses (Domínguez et al., 2002). Lexical activation also includes the retrieval of specific characteristics of the lemma related to gender and number, as well as semantic information (Zwitserslood, 1989). These processes can be completed in half a second from the presentation of the word, and are carried out in parallel with others related to sentence integration. Thus, the meaning of different words is linked in order to achieve a coherent sentence structure through syntactic and semantic combinatorial mechanisms that attribute constituents or syntagms of a sentence with thematic roles such as agent, patient, object, instrument, etc. (Hagoort, 2017). Besides linguistic information, contextual cues are also processed, including elements such as the physical environment, facial expression and gestures or emotional prosodic aspects (Van Berkum et al., 2005).

The aforementioned sequence of linguistic processes is mainly located in the left hemisphere (LH) in 95% of right-handed population and in 80% of left-handed population (Oliveira et al., 2017). Veigneau et al. (2010) carried out a meta-analysis of 128 neuroimaging articles dedicated to study the activation produced in different linguistic tasks in both left and right hemispheres (RH). They found that the activation of RH barely reached a third of the activation produced in LH. Moreover, the activated areas in RH were homotopic localizations of those in the LH, suggesting the existence of long interhemispheric connection fibers with linguistic function. Nonetheless, other intra-hemispheric connections are strongly lateralized in the brain, such as the arcuate fasciculus, which communicates the left superior temporal and inferior frontal gyri, much larger in the LH than in the RH and even non detectable in the RH of some population (Catani et al., 2007).

Generally speaking, a bunch of brain regions in the LH have been found as particularly specialized in speech processing. Thus, according to Boatman (2004), the

middle temporal gyrus and the posterior part of the superior temporal gyrus are involved in phonological acoustic processing, while the superior temporal gyrus, the inferior frontal gyrus and the inferior parietal gyrus take part in phonological decoding. In contrast, the access to meaning has been found as broadly distributed throughout the cortex; conceptual representation is indeed multimodal, and different brain areas related to sensory, motor or emotional processing are activated during semantic access, depending on the kind of information that the experience with these concepts entails (Pulvermüller et al., 2005). Furthermore, different studies on brain damage have demonstrated the specific role of the middle temporal gyrus for word comprehension, as well as the involvement of the anterior superior temporal gyrus in sentence construction, the angular gyrus in working memory during sentence processing, or the superior temporal and inferior parietal gyri in short-term memory access for spoken words (Damasio et al., 2004; Dronkers et al., 2004). Nonetheless, for a precise description of the anatomo-functional connectivity underlying language processing, a more detailed analysis of the main brain regions across the frontal, temporal and parietal cortices, as well as of the main neural pathways connecting them, is required.

Brain Regions

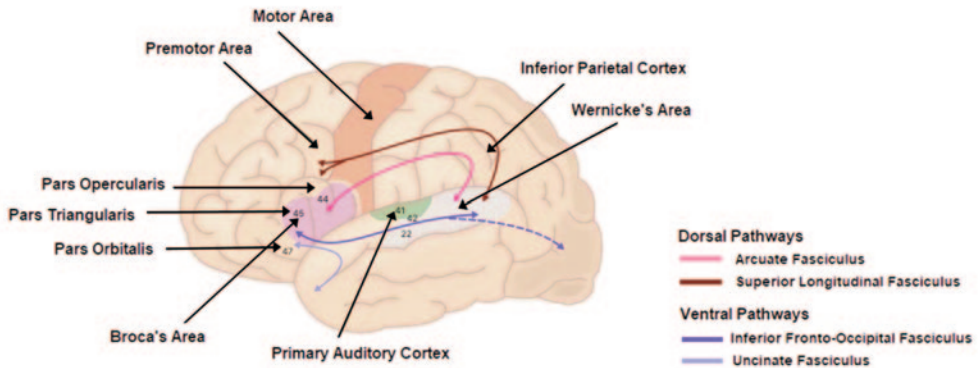
According to Friederici (2015), the linguistic areas of the *left frontal cortex* include the premotor area (Brodmann's area or BA 6), the orbitofrontal cortex (BA 47) and the inferior frontal gyrus (namely, Broca's area, which includes both pars opercularis or BA 44, divided into anterior and posterior regions, and pars triangularis, BA 45, divided into dorsal and ventral regions), see Figure 2. Whereas BA 6 is considered to be involved in phonological and articulatory processes, BA 44 and the posterior portion of BA 45 have been related to syntactic construction. The anterior portion of BA 45 and BA 47 have been given semantic functions. However, all these subdivisions are still nowadays under hot debate, especially in relation to syntactic processes, in part due to the broad disparity of materials and tasks used when investigating language processing, leading to inconsistent results across neuroimaging studies.

Regarding the *left temporal cortex*, the superior temporal gyrus, located between the lateral sulcus (Sylvian fissure) and the superior temporal sulcus, is particularly important for language (Hickok & Poeppel, 2007). Indeed, the primary auditory cortex in the middle region of the superior temporal gyrus (BA 41, 42) is responsible for processing both sounds and speech, while the anterior and posterior regions are exclusively involved in speech processing. The middle temporal gyrus performs functions related to lexical-semantic and conceptual processing, for instance about the utility of objects (Creem-Regehr & Lee, 2005).

The *left inferior parietal cortex* has been found to play a role in the active maintenance of speech information, acting as a phonological buffer (Buchsbaum et al., 2005; Kalm & Norris, 2014; Yue et al., 2019). In particular, this region has been found activated in tasks that require the use of phonological working memory, such as verbal repetition (Gruber & von Cramon, 2001). Accordingly, this region is

Figure 2

Main Brain Areas and Connecting Pathways Involved in Comprehension and Production of Language



actively involved in sentence comprehension (Grossman et al., 2002), and recruited when different elements of the speech must be maintained and related between each other, as occurs when processing distant syntagmatic elements or when those are intermediated by relative clauses.

Neural Pathways

These three different cortical areas (frontal, temporal and parietal cortices) are linked together through large white matter tracts (see Fig. 2). Two main pathways, dorsal and ventral, can be distinguished. The *dorsal pathway* connects the posterior superior temporal gyrus with the premotor area (BA 6) through the inferior parietal cortex. It is responsible for the communication between the auditory perception words and their motor articulation. It can be subdivided into two main tracts, the superior longitudinal fasciculus, which extends dorsally, and the arcuate fasciculus, in ventral plane (Friederici, 2011, 2012, 2015). The superior longitudinal fasciculus is considered responsible for the repetition of sounds, whereas the function of the arcuate fasciculus, which directly connects Broca and Wernicke's areas, is still subject to debate, although it has been mainly related to the processing of syntactically complex sentences (Friederici et al., 2006).

The *ventral pathway* can also be subdivided into two different tracts. One of them is the extreme capsule pathway, which primarily connects the middle part of the superior temporal gyrus with frontal areas (BA 45 and BA 47) and is involved in semantic processing (Saur et al., 2008). This pathway seems to be connected with a longer tract, the inferior fronto-occipital fasciculus, also with semantic functions. The second route of the ventral pathway is the uncinate fasciculus, which connects the frontal operculum with the anterior temporal cortex and whose specific function is unknown, although it seems to participate in the understanding of intelligible speech (Duffau et al., 2009; Hau et al., 2017). Some studies have also shown

the implication of this tract in syntactic processing (Humphries et al., 2005), particularly in the analysis and construction of local syntactic structures (Friederici et al., 2006). Thus, whereas the dorsal pathway is involved in complex syntactic functions, including the processing of delayed sentence elements that require the participation of the inferior parietal in their phonological decoding and maintenance, the syntactic function of the uncinate ventral pathway is restricted to the processing of local and short syntactic elements.

Language Function beyond the Left Hemisphere

Although the LH plays a critical role in both the comprehension and production of speech, linguistic functioning is not fully constrained to left brain regions. Indeed, different areas in the RH are also decisive for efficient language communication (Beeman & Chiarello, 2013; Lindell, 2006). Thus, the first step during language processing, namely the analysis of the acoustic features of the sound, is carried out bilaterally, in the primary auditory cortex located at both hemispheres (BA 41 and BA 42). Whereas the primary auditory cortex in the LH responds specifically to speech sounds, the right homolog area is activated by the tonal qualities of speech. The left primary motor cortex responds particularly fast, within 20 and 50 milliseconds after speech onset, in order to efficiently analyze the acoustic phonetic features of the spoken signal. The right primary auditory cortex, on the contrary, responds at longer latencies to the acoustic signal, between 150 and 300 ms, and is particularly involved in suprasegmental rather than phonological processing, most likely dedicated to the analysis of prosody, that is, the melody and intonation of speech (Zatorre et al., 2002). Furthermore, the contralateral area of Broca's and Wernicke' in the non-dominant hemisphere have been found to be involved in the expression and interpretation of prosodic and emotional aspects of language (Aziz-Zadeh et al., 2010; Buchanan et al., 2000; Godfrey & Grimshaw, 2016; Kotz et al., 2006; Riecker et al., 2002).

Patients with RH damage exhibit worse comprehension than patients with left lateralized brain damage, since they are able to use prosodic information to compensate their deficits during phonological decoding. For instance, Friederici, Cramon and Kotz (2007) tested the processing of prosodic features at both hemispheres by presenting sentences that could have either syntactic or prosodic incongruencies or both. They found amplitude differences in the N400, an electrophysiological component related to lexical integration difficulties, for the mismatch between prosodic and syntactic information in both healthy controls and patients with lesion at the anterior corpus callosum, thus showing the interplay between prosody and syntactic structure during speech comprehension. However, such a mismatch effect did not emerge in patients with damage at posterior corpus callosum, who only showed prosodic-independent N400 effects. These findings were taken by the authors as evidence of the key role of this structure in speech comprehension, ensuring the interaction between prosodic and pure linguistic features through interhemispheric communication.

Besides prosody, the RH is considered to be involved in other subtle but no less important aspects of language processing, such as pragmatics and the understanding of communicative intention and non-literal language, embedded in humor, metaphors, irony and other rhetorical elements (Johns et al., 2008; Mashal et al., 2005; Rapp et al., 2012). Indeed, it has been demonstrated that the processing of irony and the interpretation of the other's intentions is only possible if the RH is intact (Vigneau et al., 2010). Moreover, the elaboration of the macrostructure of discourse and the integration of contextual information are also related to the function of the RH, particularly to frontal areas.

Not only cortical regions but also subcortical structures, such as basal ganglia, thalamus or insula, have been also shown to be involved in language processing. Indeed, language comprehension is in constant interaction with attentional, memory and executive functions, which interplay is possible through connections between language-related cortical regions in the LH and subcortical structures, as evidenced by patients with damage at this level (Duffau et al., 2002; Ford et al., 2013; Kotz et al., 2009; Kuljec-Obradovic, 2003; Pichon & Kell, 2013; Radanovic et al., 2003). Studies on aphasia due to damage at the thalamic nuclei are especially interesting, given the interruption of connections between the thalamus and linguistic cortical areas. For instance, Kuljec-Obradovic (2003) reported that in patients with striatal aphasia, caused by damage in caudate and putamen, a phonetic disintegration was observed, whereas damage at the thalamic level resulted in deficits at lexical-semantic processing. Another subcortical area underlying language processing is the insula (BA 13), which strategical position allows coordination between frontal and temporal cortical areas involved in linguistic function. Although already Wernicke suggested the role of this structure in speech, the insula was out of the focus of interest in language research for more than a century (Ardila et al., 2016). The seminal work of Dronkers (1996) and other patient studies (Gorno Tempini et al., 2004; Nestor et al., 2003) recovered the interest on the relation between this subcortical region and language, showing the role of the insula in programming and coordinating complex articulatory movements during speech production (see Ackermann & Riecker, 2004, for a review). Therefore, subcortical structures seem to play an important role in linguistic processing through both subcortico-cortical connections as well as a communicative bridge between left and right cortical regions.

Reorganization of the Linguistic Network in Aphasic Patients

The aforementioned cortico-subcortical brain network dedicated to language processing can be disrupted after brain damage. A fundamental question at both experimental and clinical research levels is what is the adaptive response of this dynamic network after its interruption post brain injury. Several studies using functional magnetic resonance imaging (fMRI) have reported the overactivation of the RH as a very common brain activity pattern observed in non-fluent aphasic patients, which is due to transcallosal disinhibition after stroke (Belin et al., 1996; Hamilton et al., 2011; Naeser et al., 2004; Rosen et al., 2000; Price & Crinion,

2005). However, this overactivation could be maladaptive rather than beneficial for the patient, since right-hemispheric homologs of the left-perisylvian areas are not specialized in certain linguistic functions. Moreover, such RH overactivation usually continues during the chronic phase of the disorder, which, in turn, prevents perilesional, and importantly, still functional areas at the LH to restart language functioning.

In more detail, different stages can be differentiated in brain dynamics after brain injury. Thus, while the left perilesional areas are typically found as constantly over-activated after the stroke, contralateral brain regions in RH show a biphasic pattern, with minimal hemodynamic activation in the acute phase and predominant activation in the subacute stage, around two weeks after stroke (Saur & Hartwigsen, 2012). In contrast, LH typically shows a re-activation during the chronic phase (namely, more than one year after stroke) in those patients who exhibit successful recovery of their language function. In this line, the increased LH activation observed in chronic patients after intensive speech therapy has been found associated with the recovery of their linguistic function (Lucchese et al., 2016; Richter et al., 2008; Small et al., 1998). Moreover, studies combining neuroimaging and neuromodulatory techniques demonstrated the improvement in picture naming even two weeks after acute stroke, coinciding with increased activation of the left inferior frontal gyrus after stimulation, an improvement which is not found after stimulation of the right contralateral area (e.g. Winhuisen et al., 2005).

Therefore, such brain dynamics observed in aphasic patients have provided two important insights regarding the functioning of the linguistic network: 1) the RH plays an important role in the language network, since it directly communicates with contralateral areas in the LH, and 2) a successful rehabilitation approach must take into account not only structural state of the brain areas but also the functional changes occurred after the stroke at both acute and chronic phases.

Treatment Approaches for Non-Fluent Aphasia

Taking into account discussed findings in the neurobiology of language research, new approaches have been developed for the effective treatment of aphasic patients. In non-fluent aphasia, a strategy already showed as effective for the improvement of language fluency is to reduce the overactivation that these patients exhibit in their RH and, at the same time, to increase the activation of perilesional areas at the LH. Two main therapeutic approaches have been developed following this strategy, one applying the so-called Constraint Induced Aphasia Therapy (CIAT, Pulvermüller et al., 2001; see also Zhang et al., 2017 and Wang et al., 2020 for systematic review and meta-analysis, and Dreyer et al., 2021, for effects of CIAT at neural level) and the other applying neuromodulatory interventions through the use of techniques such as transcranial Direct Current Stimulation (tDCS, Domínguez et al., 2014) and Transcranial Magnetic Stimulation (TMS; Naeser et al., 2005a, 2012). Some of these studies have evaluated the effect of brain stimulation and its potential use in aphasia, showing a significant improvement in

chronic and subacute patients, some of them paired with language therapy (Shah-Basak et al., 2016; Nissim et al., 2020; Corrales-Quispircra et al., 2020).

Speech Therapy

The brain damage that occurs in aphasic patients does not only affect language but also motor functions, as the stroke usually produces contralateral hemiplegia. The Constraint-induced Movement Therapy (CIMT, Taub et al., 2006) has been used for the treatment of motor impairment in aphasics in order to recover the function of affected limbs. The logic under this therapeutic approach assumes that, to recover the motor functionality, a massive practice of the affected muscles is needed, avoiding the use of compensatory strategies such as, for example, by using the other non-affected limb. Forced use of impaired limbs in animal and human models has been found to produce brain reorganization, reinforcing undamaged neuronal connections and inducing activation of neural pathways and silent areas which function was interrupted as consequence of the injury. These effects have encouraged different researchers to extend the constrained-induced movement therapy into the linguistic function, following the same logic for the treatment of chronic aphasia (see Cherney et al., 2008; Pulvermüller et al., 2016; for reviews). Therefore, it has been not until very recently that conventional therapy for aphasia has started to propose treatment approaches based on the neuroscientific evidence, and hence considering the patterns of brain dynamics that follow a stroke.

The intervention proposed in the *Constraint-Induced Aphasia Therapy* (Pulvermüller et al., 2001) is based on three principles:

1. Massive practice, including 3 to 4 hours of therapy per day during 10 days
2. Progressive increase in difficulty
3. Avoidance of using any compensatory strategy such as pointing, writing, lip reading or any other way of non-verbal communication.

The therapy is implemented under naturalistic, playful sessions with the participation of 3 or 4 patients; these sessions consist in patients playing cards and asking each other to name the objects represented in the cards. Several scientific papers have reported promising results after the implementation of this therapy (e.g., Berthier & Pulvermüller, 2011; Meinzer et al., 2007; Mohr et al., 2014). For instance, Mohr et al. (2014) used fMRI to determine the level of brain changes induced in a group of patients before and after applying CIAT, analyzing bold signal in perilesional regions of the left hemisphere as well as in the homolog regions of the right hemisphere. After two-week treatment, patients showed improvements in their language function; interestingly, this change was accompanied with a significant increase of the BOLD signal in the right inferior frontal and temporal regions, particularly stronger when patients were processing highly ambiguous sentences. These findings suggest the involvement of RH in functional reorganization in aphasia and its role in the recovery of the verbal function. Other studies, in contrast, have reported a decrease in the activation of the RH and its correlation with observed clinical improvement (Richter et al., 2008), whereas others have found bilateral induced-activation (Pulvermüller et al., 2005) or increased activa-

tion in left-hemispheric regions after CIAT, particularly associated with long-term improvements in language function (Breier et al., 2009; Kurland et al., 2012). In this line, a recent meta-analysis study (Zhang et al., 2017) points out towards the effectiveness of the CIAT over conventional speech therapy for chronic, rather than for acute or subacute patients. Such effectiveness would be based on the intensive nature of this therapy, rather than on the restriction imposed on the exclusive use of verbal language.

Although the effectiveness of the CIAT has been systemically proven in scientific studies, its clinical use is still limited, likely due to the recent creation of this therapeutical approach. Nonetheless, this therapy has commenced to be adapted and standardized in other languages for its clinical use (e.g., *the Intensive Group Rehabilitation of Aphasia*, or REGIA is the first standardized version of CIAT, conducted in Spanish language Berthier et al., 2014).

Induced brain stimulation

The rationale behind the use of noninvasive brain neuromodulatory techniques for the treatment of aphasia through the application of magnetic (TMS) or electric (tDCS) stimulation is to influence the neuroplasticity of language network (see Turkeltaub, 2015, for a review). The most common practice has been to suppress the activation of the RH, though to interfere with the recovery in aphasic patients specially when the disease becomes chronic. Thus, initial studies using TMS have reported improvements in language function after applying low frequency repetitive magnetic pulses (typically 1 Hz) over the right homolog of the pars triangularis of Broca's area, considered to be mainly responsible for language inhibition (Naeser et al., 2005b; Martin et al., 2004). Many other studies have consistently reported the efficacy of this inhibitory protocol for the improvement of language function in non-fluent aphasia, evidenced across different tasks such as naming, repetition or writing (see Ren et al., 2014, for a meta-analysis). Therefore, suppressing the activation of right inferior frontal regions enables the re-activation of contralateral region in the left hemisphere, resulting in the improvement of language fluency. Regarding the application of Transcranial Direct Current Stimulation, Schjetnan, Faraji, Metz, Tatsuno and Luczak (2013) provide a very interesting review describing the rationale supporting a bi-hemispheric stimulation for the treatment non-fluent aphasia. In this approach, the anode produces excitatory effects on the LH whereas the cathode inhibits the activation on the RH. Some meta-analysis has evaluated the effect and potential use of the tDCS, indicating a significant improvement in chronic and subacute patients (Shah-Basak et al., 2016; Elsner et al., 2020; Biou et al., 2019).

However, it might be noted that the protocols used for non-invasive brain stimulation are highly variable (as well as the behavioral tasks used for clinical examination) and dependent on contextual and organic factors, thus leading inconsistent results. Indeed, improvement has been observed in language performance using protocols that activate the RH and inhibit the LH (Hamilton et al., 2011; Shah-Basak et al., 2015). Another meta-analysis has argued that dual stimulation does

not improve naming in a higher extent than left anodal stimulation alone (Elsner et al., 2020). Nonetheless, the increasing number of studies in this field may enable in the upcoming years a full validation of these therapeutical approaches as well as the definition of the stimulation protocol most suitable for each individual patient. Indeed, the combination of both approaches, with the brain induced stimulation followed by CIAT speech therapy, might be revealed as the most appropriate treatment option, with stimulation techniques inducing neuroplasticity and intensive speech therapy ensuring the consolidation of re-learned language function (Heikkinen et al., 2019). Importantly, future studies must evaluate the cost-effectiveness of each technique; for instance, tDCS is a considerably cheaper and user-friendly technique than TMS, whereas the effects of TMS are rather more focal and thus specific than in tDCS, since electrical stimulation spreads anatomically.

Conclusions

1. Research into the neurobiology of language has been impressively growing in the last 30 years, particularly with the advances in modern neuroimaging techniques; the use of these techniques both in healthy and clinical population has shown what are the specific brain structures and neural pathways involved in language function, mainly located in a left-lateralized fronto-temporo-parietal network.

2. Some linguistic processes are, nonetheless, supported by the right-hemispheric homologs of these regions, such as the analysis of speech prosody, fundamental for the correct interpretation of language, as well as by other subcortical structures, which orchestrate the coordination among these areas and prepare for speech articulation.

3. The complexity of the linguistic network and the dynamic nature of this function become evident in aphasic patients. The cortical reorganization produced after brain damage, evidenced in the overactivation of the RH as a compensation mechanism, in turn inhibits perilesional regions of the LH, thus affecting the recovery of linguistic functions.

4. New therapeutic approaches based on the most recent neuroscientific findings, such as CIAT speech therapy, the use of non-invasive brain stimulation techniques, as well as their combination, are revealed as the most promising tools for the rehabilitation of aphasic patients.

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