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Communicating with the non-dominant hemisphere

Implications for neurological rehabilitation★

Fabricio Ferreira de Oliveira, Sheilla de Medeiros Correia Marin, Paulo Henrique Ferreira Bertolucci

Department of Neurology and Neurosurgery, Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil

Abstract

Aphasic syndromes usually result from injuries to the dominant hemisphere of the brain. Despite the fact that localization of language functions shows little interindividual variability, several brain areas are simultaneously activated when language tasks are undertaken. Mechanisms of language recovery after brain injury to the dominant hemisphere seem to be relatively stereotyped, including activations of perilesional areas in the acute phase and of homologues of language areas in the non-dominant hemisphere in the subacute phase, later returning to dominant hemisphere activation in the chronic phase. Plasticity mechanisms reopen the critical period of language development, more specifically in what leads to disinhibition of the non-dominant hemisphere when brain lesions affect the dominant hemisphere. The non-dominant hemisphere plays an important role during recovery from aphasia, but currently available rehabilitation therapies have shown limited results for efficient language improvement. Large-scale randomized controlled trials that evaluate well-defined interventions in patients with aphasia are needed for stimulation of neuroplasticity mechanisms that enhance the role of the non-dominant hemisphere for language recovery. Ineffective treatment approaches should be replaced by more promising ones and the latter should be evaluated for proper application. The data generated by such studies could substantiate evidence-based rehabilitation strategies for patients with aphasia.

Fabricio Ferreira de Oliveira★, M.D., M.Sc., Universidade Federal de São Paulo (UNIFESP), Escola Paulista de Medicina, Departamento de Neurologia e Neurocirurgia, Rua Botucatu 740, Vila Clementino, CEP 04023-900, São Paulo, SP, Brazil, fabricioferreiradeoliveira@hotmail.com.

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Research Highlights

- (1) Language processing takes place mostly in interlinked serial and parallel processing areas of the dominant hemisphere.
- (2) The non-dominant hemisphere has a stereotyped role during language recovery after brain injuries, which may be modulated by rehabilitation strategies.
- (3) Plasticity mechanisms lead to disinhibition of the non-dominant hemisphere when brain lesions affect the dominant hemisphere.
- (4) Currently available rehabilitation therapies have shown limited results for efficient language improvement, while randomized controlled trials that evaluate well-defined interventions in patients with aphasia are required for development of evidence-based rehabilitation strategies that enhance neuroplasticity mechanisms in the non-dominant hemisphere.

INTRODUCTION

During the evolution of Cognitive Neurology, the first evidence for localization of higher brain functions arose from studies of language disorders^[1]. Since the end of the nineteenth century, aphasic syndromes had been considered to be mostly mediated by specialized areas of the dominant hemisphere of the brain^[2]. However, it is currently known that, while localization of language functions shows little interindividual variability, several brain areas in both hemispheres are simultaneously activated when a language task is undertaken^[3-5].

Ambidextrous individuals usually have bilateral language dominance, while those with left, bilateral, or right hemisphere language representation do not differ significantly with respect to verbal fluency, linguistic processing, or intelligence, as well as with regard to the homology of anatomical and functional organization of language networks in either hemisphere^[6]. More than 95% of right-handed individuals, as well as more than 70% of left-handed individuals, have left hemisphere dominance for language^[1, 5]. Aphasic syndromes usually result from injuries to the dominant hemisphere^[7]. The exact role of the non-dominant hemisphere in language processing during recovery from brain injury is yet to be more thoroughly evaluated.

The objective of this paper is to investigate the role of the non-dominant hemisphere for language rehabilitation strategies in patients with acquired forms of aphasia.

THE GENESIS OF LANGUAGE LATERALIZATION

Three large networks interact to connect language with conceptual information^[1]. Broca's and Wernicke's areas, the insular cortex, the head of the caudate nucleus and the putamen in the dominant hemisphere form the language implementation system, which analyzes auditory signals to activate conceptual knowledge and support phonemic and grammatical construction while controlling production of speech. This system is surrounded by a mediational system, composed of several regions distributed among the parietal, frontal and temporal association areas, acting as brokers between the language implementation system and the so called conceptual system. The conceptual system is composed of a group of regions spread throughout the association areas. It is important to note that

bidirectionality is an important attribute of the arcuate fasciculus, which connects areas of the sensory cortex (including Wernicke's area) with prefrontal and premotor areas (including Broca's area) in the dominant hemisphere^[7]. This leads to greater difficulties in repetition when considering the role of the non-dominant hemisphere in the rehabilitation of language disorders for patients with injuries to the dominant hemisphere^[7-8].

Subcortical structures are also known to contribute to the organization of language^[1, 9], in view of their reciprocal connections with cortical language areas. This is particularly true for the lexical-semantic processing in inferior, lateral and posterior thalamic nuclei, and also for the phonetic processing for fluency in the striatal structures of the dominant hemisphere^[9]. Also, attention and executive functions may be affected when the thalamus in the dominant hemisphere is injured, and visual-spatial orientation may be particularly impaired when lesions occur in the thalamic nuclei of the non-dominant hemisphere^[10]; such impairments may affect the linguistic performance of patients after brain injury. Disconnection syndromes may occur when lesions involve the thalamus and the basal nuclei, the structures that generate subcortical aphasias.

Language has three highly interrelated and integrated components: cognitive, linguistic, and pragmatic. Within this context, aphasia is defined as an acquired impairment in language production and comprehension and in other cognitive processes that underlie language. Aphasia causes problems with any or all of the following: speaking, listening, reading, writing and gesturing abilities. Some manifestations of aphasia include: difficulties in using words and sentences (expressive aphasia); problems in understanding others (receptive aphasia); and difficulties in both using words and understanding (global aphasia). These manifestations may be characterized by: fluency impairment; difficulty to comprehend and/or produce words; phonemic distortion or exchange of semantically related words (phonemic or semantic paraphasias, respectively); difficulty to name objects (anomia) or to recall words during conversation; and impairment in social communication skills (pragmatic language). Reading and writing are usually affected in patients with aphasia, while phono-articulatory function and consciousness are relatively preserved. Patients with aphasia communicate in ways that make them feel like they are in a new world, with peculiar forms of expression and understanding. The severity of communication difficulties depends on the location of the brain injury and other factors will be further discussed.

Table 1 Classification of language disturbances

Type of disturbance	Spontaneous speech	Fluency	Comprehension	Repetition	Naming	Other signs	Lesion localization (dominant hemisphere)
Broca's aphasia	Poor, with effort, paraphasias, agrammatism	Impaired	Preserved	Impaired	Impaired	Hemiparesis, apraxia of mouth and hand	Posterior-inferior frontal
Wernicke's aphasia	Logorrheic, with paraphasias and neologisms	Preserved	Impaired	Impaired	Impaired	Homonymous hemianopia, apraxia, anosognosia	Posterior-superior temporal
Conduction aphasia	Normal (phonemic mistakes)	Preserved	Preserved	Impaired	Preserved	Hemi-hypoesthesia, hemianopia	Arcuate fasciculus-supramarginal gyrus
Global aphasia	Poor (mutism), restricted to simple verbal stereotypes	Impaired	Impaired	Impaired	Impaired	Hemiparesis, hemianopia, hemi-hypoesthesia, apraxia	Perisylvian region (middle cerebral artery territory)
Semantic aphasia	Normal (difficulty in finding words)	Preserved	Preserved	Preserved	Impaired	Homonymous hemianopia	Inferior parietal (angular gyrus)
Transcortical motor aphasia	Poor (mutism), with great latency at responses, echolalia, perseveration	Impaired	Preserved	Preserved	Impaired	Eventual hemiparesis (crural involvement) and grasp reflex	Anterior and superior to Broca's area (supplementary motor area)
Transcortical sensory aphasia	Normal (semantic jargon)	Preserved	Impaired	Preserved	Impaired	Eventual hemianopia and visual agnosia	Watershed areas of middle cerebral artery and posterior cerebral artery
Mixed transcortical aphasia	Mutism	Impaired	Impaired	Preserved	Impaired	Eventual hemianopia, visual agnosia and hemiparesis	Watershed areas of middle cerebral, anterior cerebral and posterior cerebral arteries
Apraxia of speech	Articulatory difficulties, phonetic mistakes	Impaired	Preserved	Impaired	Impaired	Eventual apraxia or bucofacial and tongue paresis	Inferior part of pre-central gyrus and nearby areas
Verbal deafness	Normal	Preserved	Impaired	Impaired	Preserved	Absent	Middle third of superior temporal gyrus
Thalamic aphasia	Normal or with paraphasias	Preserved	Preserved or discretely impaired	Preserved	Impaired	Dysarthria, initially with mutism	Thalamus in the dominant hemisphere
Subcortical aphasia (non-thalamic)	Poor, with great latency at responses, echolalia, perseveration	Preserved	Preserved	Preserved	Impaired	Dysarthria, hypophonia	Basal nuclei in the dominant hemisphere

Table 1 shows the most important aphasic syndromes, as well as the most likely brain injury sites to result in these language disturbances^[2, 11].

Language is dependent on an interlinkage of serial and parallel processing areas in distinct brain regions considered to be elementary processing units^[1, 5]; therefore, language processing takes place mostly in the dominant hemisphere, which is usually the left one. Development of hemisphere dominance for language processing is related to the specificity of synaptic connections established before and after birth, but the

exact point in time when this dominance takes place is still unknown^[1]. Speech production develops simultaneously with speech perception during infancy. Postnatal neuronal plasticity directs the formation and maintenance of active neural connections while pruning the aberrant ones, leading to the construction of a language network that allows humans to communicate with one another^[12]. Though aphasia and apraxia are dissociated from each other, they are often comorbid, and there is also evidence for left hemisphere lateralization in terms of praxis at the hand-independent level^[13].

Spoken language is only one of several language skills mediated by the dominant hemisphere. Contrariwise, affective aspects of language such as intonation (prosody) are processed in the non-dominant hemisphere, mirroring the logical organization of language content in the dominant hemisphere^[1, 5]. Irony, musical interests, metaphors and intentions can only be appreciated when the non-dominant hemisphere is intact^[1]. The abilities for elaboration of discourse macrostructure and for contextual integration of information are basically non-dominant hemisphere functions, particularly related to the frontal lobe^[10], as well as the ability for single word reading in patients recovering from aphasia.

Spatial orienting is usually a function of the non-dominant hemisphere, analogous to the predominant development of language functions in the dominant hemisphere. The non-dominant hemisphere would be more influenced by incoming visual information along its genesis, and specializing in attentional processes rather than in language^[14]. Body neglect has been described as one of the most important factors affecting length of hospital stay and discharge destination (home or elsewhere) for stroke patients^[15]. However, neglect may also result from acute damage to the dominant hemisphere, represented in areas typically serving language functions, namely the superior and middle temporal gyri, the inferior parietal lobule, and the insula^[14]; these patients may present both neglect and aphasia. Patients with left hemisphere lesions who develop spatial neglect usually fail to address stimuli located on the right, unlike patients with the typical neglect and anosognosia resulting from right hemisphere lesions, who fail to address stimuli located on the left side and tend to be more severely handicapped.

The critical period for language development extends from infancy to early adolescence. The processes involved in learning the sound patterns of a new language alter the brain early in development, leading to the production of words in a way that will affect the brain for life^[1, 5]. Maturation and experience are the major factors leading to the development of the critical period for language, the first one "opening" the window for learning, and the second one "closing" it^[1]. However, later in life the process of learning a new language (or relearning it, in case of patients with aphasia) can be improved by mimicking the critical components of early learning: long periods of listening in a social contextualization, information both visual and auditory, and exposure to simplified speech.

The plasticity of the critical period for language in infancy can be distinguished from plasticity in adulthood by its magnitude and by the ease of its triggering^[1, 16]. However, plasticity may still develop in adulthood because of mechanisms that lead to reopening of the critical period of language development, more specifically in what leads to disinhibition of the non-dominant hemisphere when brain lesions affect the dominant hemisphere^[1, 17]. This is one of the most important mechanisms for rearrangement of neural networks during recovery from brain diseases. The speed of language rehabilitation in such cases is, however, much slower, since structural stability overcomes plasticity in the adult brain – axonal growth and synaptic formation are not so easily undertaken by then. It is widely known that neuronal regeneration is poor in the central nervous system of mammals, more specifically considering that glial scars inhibit axonal regeneration while limiting the lesion size and reducing inflammation (an adaptive response that prevents the dissemination of the brain injury)^[1]. Strategies that target the role of the non-dominant hemisphere for language could lead to more efficient results in terms of neurological rehabilitation, especially considering that the value of perilesional recruitment of neurons in the dominant hemisphere for language recovery is still controversial^[1, 18].

Mechanisms of language recovery after brain injury to the dominant hemisphere seem to be relatively stereotyped. There are increased activations of homologues of language areas in the non-dominant hemisphere, and of perilesional areas of the dominant hemisphere, including compensatory recruitment of new areas and of language areas that were spared^[19]. Sometimes, there may also be dysfunctional activation of the non-dominant hemisphere interfering with language recovery due to increased and deleterious transcallosal inhibition of the already damaged dominant hemisphere^[20]. It seems that the areas recruited for a particular language task change over the course of recovery, with minimal elicited activation (or hemodynamic response) during the language task in the acute stage, predominant non-dominant hemisphere activation in the subacute stage, and a return to predominant dominant hemisphere activation in the more chronic stage in patients who show good recovery of the task^[3, 20].

A native language and a second language that shares its universal grammar can assume different region-specific processing rules according to the time when they were learned. Hemisphere lateralization of language seems to

depend on the bilingual status of the individuals, with bilateral hemispheric involvement for both languages of early bilinguals (who learned such languages during early infancy), left hemisphere dominance for language of monolinguals, and also left hemisphere dominance for both languages of late bilinguals^[21]. If both languages are learned during infancy, their fluency tends to activate indistinguishable sites in Broca's area; however, if the second language is acquired during adulthood, it is usually represented in a separate region in Broca's area^[22]. It is possible that the mechanisms that generate this duality could also be present in the non-dominant hemisphere, leading to interventions that could successfully make patients communicate better after brain injury. However, it is still not known whether the left hemisphere dominance for language is present at birth, or if a specific linguistic specialization based on experience is required for the functional separation of the hemispheres.

STRUCTURE-FUNCTION CORRELATIONS

Regardless of etiology, focal brain lesions are the most important models for the study of correlations between structural changes and linguistic functions. Strategic lesions may produce aphasic syndromes regardless of the injury size. The angular gyrus in the dominant hemisphere integrates functions from several other areas of the brain, accounting for left-right orientation, constructional praxis, naming, reading and writing (the spatial representation of words), calculation and finger recognition^[23]. While lesions to the angular gyrus may result in semantic aphasia, patients with brain lesions often show double dissociations between their abilities to name objects and actions, suggesting that entity and event knowledge are mediated by different neural networks^[24]. Involvement of the insula or subinsular area of the dominant hemisphere tends to produce phonemic disintegration and disturb speech fluency, resulting in apraxia of speech and transcortical motor aphasia^[25]. Apraxia of speech has always been described with lesions to the dominant hemisphere, more specifically the left superior precentral gyrus of the insula, and usually follows nonfluent aphasic syndromes rather than being a sole finding, but tends to be more severe when premotor and supplementary motor areas of the same hemisphere are also involved^[26].

Alexia without agraphia refers to impaired reading in the presence of spared writing and relatively spared recognition of words spelled aloud, often resulting from a

combination of lesions in the left occipital cortex resulting in right homonymous hemianopia (such that all visual information is initially processed in the right occipital cortex) and in the splenium of the corpus callosum preventing visual information in the right hemisphere from being transferred to the left hemisphere language networks^[3]. Lesions usually include connections of the visual word form area, a modular area located in the lateral occipitotemporal sulcus of the dominant hemisphere which is mostly responsible for orthographic reading-specific processes of the brain, and partially selective for written strings relative to other categories such as line drawings^[27-28]. Many of these patients are also unable to name visual stimuli, although they can name the same items from tactile exploration or in response to verbal description, a pattern known as "optic aphasia" (though not exactly classified as an aphasic syndrome).

Language networks are so important for daily living that a direct relationship exists between lesion size and both language recovery and mortality^[20, 29-32]. Global aphasia is usually a stronger predictor of mortality for stroke patients when present in the acute phase than other language disorders^[32], and has also been shown to bring an unfavorable prognosis to post-stroke mobility recovery, something that could be phylogenetically related to the simultaneous development of language networks and motor gesture activity in earlier primates^[17, 31-33]. Language recovery for stroke patients is usually faster in the first months, more importantly for fluency than for speech comprehension, an unwanted result considering that impaired comprehension in the acute stroke patient usually leads to a longer hospital stay^[29-31, 34].

Age, education, depression, lesions in the dominant hemisphere and cortical injuries are other important prognostic factors for language recovery after a first stroke^[8, 29, 31, 34-35]. Education may lead to distinct communication forms that allow some high schooling patients with aphasia to communicate better than low schooling individuals without brain injuries. Along with other environmental and cultural influences, schooling might modify brain organization and connections between cortical structures in both hemispheres, leading to better performance in language tests, and also protecting patients from post-stroke dementia. It has been demonstrated that the better the response to language tests involving writing, the likelier it is for a patient with a non-fluent aphasia to have a good evolution^[36].

When patients with aphasia present with cerebrovascular subcortical injuries, prognosis is much more favourable the less likely one is to find that there has been cortical hypoperfusion^[31, 34]. Lesion size and cortical hypoperfusion in the acute phase are significant risk factors for bad prognosis of aphasia. Even though lesion size is an important prognostic factor for depression and language recovery^[8, 31], more notably if there is salvageable tissue (penumbra) involved^[37], lacunar infarctions and leukoariosis are also able to aggravate language dysfunction^[38].

It is believed that recovery of language after stroke is produced primarily by arterial recanalization or expansion of collaterals, giving rise to an enhanced flow in the hypoperfused cortical penumbra^[39], and secondarily by mechanisms related to the disinhibition of the uninjured hemisphere^[1]. The dominant hemisphere supposedly modulates the inhibition of the activation of arousal systems by the non-dominant hemisphere and enhances emotional behaviors with social communicative purposes, so that patients with injuries to the dominant hemisphere have an increased visceral-autonomic response to stimuli, more specifically if aphasic syndromes are present; this leads to phenomena such as the catastrophic reaction, an outburst of frustration, depression, and anger when the patient is confronted with a task, which is almost exclusively present in the acute stroke phase when the dominant hemisphere is injured and aphasia is present^[40].

In cases of right hemisphere lesions, patients often produce inappropriately stressed speech, with awkward timing and intonation, and flattened emotionality. These patients also have difficulty to interpret the mood and emotional cues in the speech of others, and their narrative is usually incoherent when ordering sentences^[1].

Ictal evaluation of language may be able to localize complex partial seizure commencement in patients with epilepsy^[41], and some studies with patients who had infancy or adolescence onset of epilepsy have shown evidence of plastic processes affecting language lateralization. While speech processes activate superior temporal regions bilaterally, there may be convergence to a right hemisphere dominant pattern for language in some patients with left mesial temporal sclerosis or neoplastic diseases (inter-hemispheric reorganization), contrary to what usually happens in the uninjured brains of right-handed individuals that have developed left

hemisphere dominance^[42-44]. In some patients with epilepsy, reorganization of language results in receptive and expressive functions showing divergent hemispheric dominance^[42], while in others a perilesional (intra-hemispheric) reorganization may also be seen^[44]. This is an example of chronic reorganization of language functions^[43], unlike the changes that occur after acute brain injury.

The presentation of neurodegenerative diseases usually comprises language disturbances as a major feature. Visual confrontation naming, reading comprehension and auditory comprehension are frequently impaired in mild stages of dementia due to Alzheimer's disease, further leading to fluency deficits and eventually mutism in late stages^[45]. Impairments in phonologic processing are typically found in corticobasal degeneration, leading to severe aphasia in more advanced stages^[46]. Primary progressive aphasia is a syndrome characterized by progressive loss of language functions with initial sparing of other cognitive domains, resulting from a circumscribed atrophic process in language areas, and is classified into the following variants: non-fluent, semantic, or logopenic^[47].

The logopenic variant of primary progressive aphasia, with hesitant anomie speech, word retrieval and sentence repetition deficits, features left posterior perisylvian or parietal atrophy and usually evolves to dementia due to Alzheimer's disease in advanced stages^[48]. By comparison, apraxia of speech is one of the initial features of progressive non-fluent aphasia, which typically involves the left posterior fronto-insular region, is a better predictor of a tauopathy and may evolve to corticobasal degeneration in later stages, while the semantic variant of primary progressive aphasia develops early involvement of the anterior temporal lobes (predominantly in the left), is associated with ubiquitinated inclusions and usually evolves to the classical form of semantic dementia or to behavioral variant frontotemporal dementia^[49]. Features that differentiate the variants of primary progressive aphasia in the early stages may lose their distinctiveness as the degeneration advances^[50].

It has been demonstrated that the right posterior superior temporal sulcus structures show an increase in activity both in patients with primary progressive aphasia and in those with dementia due to Alzheimer's disease, correlating positively with the performance in language tasks^[51]. However, in view of the underlying neurodegenerative mechanisms, the effectiveness of

rehabilitation strategies tends to be very limited.

In spite of all the controversy regarding neuronal plasticity after brain injury, most rehabilitation interventions are still insufficient to address patients' needs in terms of independence and recovery; hence, it is important to optimize therapies that rely on the best outcomes for such patients.

IMPLICATIONS FOR NEUROLOGICAL REHABILITATION

Aphasia is caused by stroke in more than 80% of all cases^[2], and up to 40% of stroke patients may have aphasia in the acute phase^[12, 23, 29, 34]. In terms of rehabilitation, when compared with stroke patients without aphasia, patients with aphasia have a lower quality of life, are more distressed, and participate in fewer activities^[52]. For stroke patients with aphasia, the outcomes of rehabilitation therapy for speech and language disorders seem to be proportional to the time invested in it, with patients receiving more than 8 hours of therapy per week improving more than those who receive less than 3 hours per week in the first 3 months after brain injury^[34, 53]. Semantic and phonological treatment of anomia also seem to be beneficial for functional communication^[53]. Overall cognitive-linguistic therapies are recommended during acute and chronic rehabilitation for language deficits secondary to dominant hemisphere stroke and brain trauma^[52-54], but focal inhibition of homologous language areas of the non-dominant hemisphere using transcranial magnetic stimulation has been losing power as controversy questions its role over sustained improvement of aphasia^[55].

Pharmacological therapy of aphasia has been employed in small studies by the use of drugs such as cholinesterase inhibitors, memantine, piracetam, bromocriptine, fluoxetine, zolpidem and amphetamines, with or without concomitant speech therapy. Patients with post-stroke aphasia and neurodegenerative diseases have been evaluated. However, since results were unconvincing and the benefits have not been fully demonstrated, large-scale randomized clinical trials are needed to support such therapy^[31].

For patients in the chronic phase after brain trauma, the training of social skills based on pragmatic communication behaviors (listening, starting a conversation) and social perception of emotions and

social inferences, along with psychotherapy for emotional adjustment, seems to be useful for patients' ability to adapt to the social context of conversations^[54]. Recovery and reorganization of language networks is use-dependent and must be achieved by the active participation of patients as much as possible^[12]. Computer-based interventions along with group-based interventions may be considered for remediation of language deficits after dominant hemisphere stroke and for social-communication deficits after brain trauma^[54].

In cases of unilateral spatial neglect, current evidence recommends visual scanning training and visual-spatial motor training for better performance and independence after right hemisphere stroke^[53-54]. The use of isolated computer exercises to treat left neglect after stroke does not appear effective^[54]. These results are more evidence-based than those found for language rehabilitation.

Musical features are usually processed in brain areas which are different from the ones related to spoken language and speech, bringing about some patients with non-fluent aphasia being able to sing while unable to speak^[56]. Melodic intonation therapy and cued singing are options for patients with non-fluent aphasia, resulting in strengthened breathing and vocal ability, improved articulation and prosody of speech, and increased word retrieval and communicative behaviours in general^[57]. Melodic intonation therapy results in an increase in white matter fibres and volume in the non-dominant arcuate fasciculus correlating with patient improvement^[20]. Rhythmic acoustic and social cues may be responsible for the enhancement of speech networks for such patients, possibly involving the mirror neuron system in the context of neural networks distributed throughout the non-dominant hemisphere^[16, 56-57].

The evidence for rehabilitation strategies is stronger for compensation of aphasia than for the level of functional activities, participation, or life satisfaction. The non-dominant hemisphere for language has a critical role during recovery from aphasia, probably related to the lexical learning itself present in healthy subjects and to mechanisms of brain plasticity; recruitment of networks in the non-dominant hemisphere is believed to occur concurrently with attempts to repair the damaged original language networks in patients with aphasia^[4, 32]. It is generally accepted that there is greater activity in the non-dominant hemisphere in post-stroke aphasia compared to healthy subjects, subject to modulation by therapy and verbal learning^[4, 17]. Nevertheless, it has

been shown that the supplementary motor area in both hemispheres is particularly activated when patients try to speak aloud auditorily presented stimuli, or even during silent verb generation, suggesting that this area is part of a language network that includes a subvocal rehearsal system and a phonological store^[4]. The additional activation of non-dominant hemisphere regions may be interpreted as a further involvement of functionally connected and parallel processing networks which, while holding some importance for speech, are usually not needed for language processing in the uninjured brain.

Children learn to read by way of the recycling hypothesis, which states that plastic neuronal changes leading to word representations in the dominant fusiform gyrus occur in the context of strong constraints evolutionarily imposed to this cortical area that led it to previously specialize in object processing, considering both the genetic background and the education-induced changes over the receptor densities and connectivity patterns of its cortical networks^[28]. For patients with aphasia, it is possible that such mechanisms might also develop in the adult non-dominant hemisphere when it is exposed to rehabilitation therapy.

Several approaches to the rehabilitation of aphasia are currently available^[53-54]: the disorder-oriented approach aims at restoring linguistic processing by providing linguistic treatment; the functional treatment approach aims to achieve an optimal level of communication, given the linguistic deficits; and the participation-oriented treatment emphasizes on dealing with the consequences of aphasia by removing social barriers. All these approaches must be combined for an optimal result, as much as the control of other cognitive and behavioural deficits that might be present, since executive dysfunction is an important factor to jeopardize neurological rehabilitation^[58], and cognitive impairments can impact the construction of language, new verbal learning, and transactional success^[52].

Converting handedness tends to induce plasticity mechanisms that lead to reorganization of specific brain areas. When forced to use the right hand, left-handers show an increase in movement-related activity in the primary sensorimotor hand area and posterior premotor cortex of the left hemisphere associated with the relative left-to-right shift in hand preference^[59]. Considering the relationship between language and hand function, global rehabilitation strategies might achieve better results than solely the rehabilitation of language for patients with multiple neurological deficits^[17]. During skill learning,

involvement of the ipsilateral hemisphere may influence the magnitude of intermanual transfer regardless of the degree of handedness, which suggests that approaches that involve both hemispheres during language rehabilitation may be more efficacious as well^[60]. The double dissociation between visual control of action and handedness, leading to independent hemispheric specialization for both functions, may also lead to better results in motor rehabilitation regardless of the presence of aphasia^[61].

Concerning rehabilitation strategies, the theory of the mirror neuron system implies in understanding others' actions by means of an automatic matching process that links observed and performed actions. Mirror neurons discharge during the execution of goal-directed manual and oral actions, as well as during the observation of the same actions undertaken by other individuals^[16]. Constraint-induced principles, also known as use-dependent learning principles, comprise forced-use therapy of aphasia in small steps during a shaping process, believed to allow for gradual and facilitated takeover of lost functions by the language-related areas of the intact hemisphere using a highly intensive treatment protocol, administered in a behaviourally relevant context and accompanied by reinforcement strategies in a concentrated fashion^[33]. An individualized repetitive intensive training seems to result in the highest efficacy for patients with aphasia and dysarthria, as it leads to strengthened neural connections between task relevant brain regions, which are thought to be the neural basis of learning and recovery from brain injury. The most important areas in which mirror neurons seem to be located in humans are those that are activated during observation and execution of speech, such as the inferior precentral gyrus, the inferior parietal lobule, and the pars opercularis of the inferior frontal gyrus^[16]. In view of the fact that words whose retrieval is facilitated by gestures are more likely to be analogically encoded in a multimodal representation including sensory-motor features, it is likely that action observation leads to organizational changes in the brain and may participate, via the mirror neuron system, in the relearning of language fluency and comprehension^[16, 33].

The inferior frontal gyrus seems to be an important element for language recovery after a stroke. Activation of the non-dominant inferior frontal gyrus seems to be essential for word retrieval from long-term memory for some patients with vascular aphasic syndromes, and also for lexical learning in individuals without brain injuries^[62], though its compensatory potential appears to

be less effective than in patients who recover inferior frontal gyrus function in the dominant hemisphere^[63]. This could reflect the activation of mirror neurons which are apparently concentrated in the inferior frontal gyrus of both hemispheres, since patients with left inferior frontal lesions tend to recruit the right inferior frontal gyrus more reliably than those without such lesions^[19].

Considering that functional communication usually improves spontaneously over the first months after stroke^[31], also due to repeated practice of everyday communication^[30], the benefits of early aphasia rehabilitation are still uncertain. Ineffective treatment approaches should be replaced by more promising ones and the latter should be evaluated for proper application. The fact that some patients show better response to speech and language therapy than others might be indicative of some unidentified cognitive impairments that impact their ability to recover from aphasia.

CONCLUSION

Despite the heterogeneity of language disorders, there is a clear need for large-scale randomized controlled trials that evaluate well-defined methodologies of intervention in patients with aphasia. Standardized test instruments and protocols for imaging tools need to be improved to properly characterize the components of normal speech and language, hence enabling the identification of patient cohorts with specific aphasic syndromes, as well as neuroplasticity mechanisms that elucidate the role of the non-dominant hemisphere for language recovery. The data generated by such studies could substantiate evidence-based rehabilitation strategies for patients with aphasia.

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Correction Announcement

The order of the authors' affiliations of the article entitled "Bone marrow-derived mesenchymal stem cells increase dopamine synthesis in the injured striatum" published in *Neural Regeneration Research* [2012;7(34):2653-2662] was mistaken during information collection by Web of Science.

The original author list and affiliations published in print are as follows:

"Yue Huang¹, Cheng Chang², Jiewen Zhang¹, Xiaoqun Gao²

1 Department of Neurology, Henan Provincial People's Hospital, Zhengzhou 450003, Henan Province, China

2 Department of Anatomy, Zhengzhou University, Zhengzhou 450004, Henan Province, China"

Hereby Certified!

Editorial Department of Neural Regeneration Research