Chapter 24

Neurophysiology of Language Pathologies

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Abstract

Language- and speech-related disorders are among the most frequent consequences of developmental and acquired pathologies. While classical approaches to the study of these disorders typically employed the lesion method to unveil one-to-one correspondence between locations, the extent of the brain damage, and corresponding symptoms, recent advances advocate the use of online methods of investigation. For example, the use of electrophysiology or magnetoencephalography—especially when combined with anatomical measures—allows for in vivo tracking of real-time language and speech events, and thus represents a particularly promising venue for future research targeting rehabilitative interventions. In this chapter, we provide a comprehensive overview of language and speech pathologies arising from cortical and/or subcortical damage, and their corresponding neurophysiological and pathological symptoms. Building upon the reviewed evidence and literature, we aim at providing a description of how the neurophysiology of the language network changes as a result of brain damage. We will conclude by summarizing the evidence presented in this chapter, while suggesting directions for future research.

Key words EEG, ERPs, TMS, Aphasia, Parkinson's disease, Specific Language Impairment

1 Introduction

Any brain injury or developmental disorder resulting in an impairment of language and/or of its vocal expression, speech, comes at a high price for a person's quality of life. Given the individual burden and societal cost of these pathologies, research has extensively focused on identifying pathology-specific neurophysiological markers, on exploring neural mechanisms supporting recovery of function, and on developing interventions to restore functionality to premorbid levels. Classic research on language- and speech-related pathologies primarily targeted the metabolic, hemodynamic, and structural brain levels in an attempt to link symptomatology to the location of its organic cause. While this approach contributed to significant advances in neuropsychology and neurolinguistics, it underestimates the fact that speech—as many other

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human activities—unfolds in time; hence, significant insight may come from the analysis of speech and language by employing electrophysiological measures, such as electroencephalography (EEG; e.g., [1–3]) and magnetoencephalography (MEG; e.g., [4, 5]), capable of tracking spontaneous activity (e.g., during resting state) and stimulus-driven activity (evoked responses) with high temporal resolution. Yet further insight might come from techniques capable of interfering with ongoing brain activity, such as Transcranial Magnetic Stimulation (TMS) and Direct-Current Stimulation (tDCS; e.g., [6–8]). More and more frequently, however, multiple techniques allowing both high temporal resolution and spatial resolution—for example, electrophysiological and structural recordings—are combined to reach an even more comprehensive and integrated account of the symptomatology and neurobiology of language and speech disorders arising as a consequence of both developmental and acquired brain damage [9, 10].

The development of such an integrative approach in the study of speech and language pathologies, however, does not end with adopting integrated methods, but should also consider the composite nature of the study object: Language is a complex and multilayered system, whose components are spread across several hubs, ancillary nodes, and connections in a distributed cortico-subcortical network [11, 12]. Lesions occurring in either hubs or connections of this system may result not only in local alterations of the underlying neurophysiology, but in a global updating of the entire system [13]. For example, both an increase in delta amplitude—a slow EEG band usually associated with deep sleep and rest—and a decrease in the beta band, a marker of active brain processing—have been described as markers of brain damage across a variety of pathologies and symptomatology, including aphasia [14]. While this evidence is suggestive of plastic neurophysiological alterations that are independent of the pathological mechanism, specific markers (e.g., a decrease in beta range activity in response to linguistic stimuli, typical of post-stroke aphasia—*see* Subheading 2.1) are bound to depend upon several factors.

This chapter aims at targeting these factors to provide a comprehensive account of speech- and language-related pathologies. We will discuss the consequences of damage with diverse etiologies (e.g., focal or diffuse, developmental, affecting perception or production); further, we will explore the specific and often neglected contribution of subcortical structures in the language network. Building upon the reviewed evidence and literature, we will sketch a description of how the neurophysiology of the language network changes as a result of brain damage. We will conclude by summarizing the evidence presented in this chapter, while suggesting directions for future research.

2 Forms of Language Disorders

Human language and its vocal expression, speech, rely on a complex system of several cortical hubs and their underlying white-matter connections [15–18]. Yet another important part of the circuit is represented by the basal ganglia, a group of subcortical nuclei which form extensive networks with near and distant cerebral regions (e.g., pre-supplementary motor area—preSMA, cerebellum [19–21]). Lesions at both cortical and subcortical levels may result in speech and language pathologies; however, several additional factors may have an impact on the resulting symptomatology and recovery trajectory. One such factor is whether the lesion is focal (i.e., localized) or diffuse (i.e., widespread): Diffuse damage typically entails more severe deficits, although important exceptions need to be discussed. The age of the patient is an equally important aspect to consider: Not only may lesions or deficits occurring during childhood have significantly different outcomes from their adult equivalents, but this very plastic period of life may cause specific impairments whose onset is not typical in adulthood. Finally, language pathologies may be classified depending on whether they affect primarily the system input (i.e., perception) or the output (i.e., production).

2.1 Pathologies Due to Focal Damage

Focal brain damage is caused by spatially confined injury in a specific cortical or subcortical region, either in the gray or white matter of the brain. While neuronal loss and cerebrovascular damage represent primary consequences, ischemia or cascades of cytotoxic effects may further complicate the clinical picture [22]. The cause of focal brain damage may be either traumatic (e.g., blow to the head) or organic (e.g., tumor and ischemic or hemorrhagic stroke). In either case, the symptomatology mostly depends on where the damage occurred and is typically highly circumscribed to specific functions (but see below for important exceptions when the damage occurs in the white matter). The two most famous examples of localized damage affecting linguistic functions trace back almost two centuries to the studies of Paul Broca (1865) [23] and Carl Wernicke (1874) [24]: By correlating behavioral symptoms with post-mortem pathological findings, Broca identified a brain region involved in speech production in the third convolution of the inferior frontal gyrus (IFG), while Wernicke discovered the location of the brain's hub for speech comprehension in the posterior superior temporal gyrus. Nowadays, researchers can map behavioral symptoms to brain lesions in vivo, due to high-quality structural magnetic resonance imaging. This approach, called lesion-symptom mapping (LSM, [25–27]), can be further combined with electrophysiological methods to provide a comprehensive account of plastic reorganization following focal damage.

Localization-based investigations (both post-mortem and in vivo) revealed that speech- and language-related deficits are most commonly encountered as a consequence of left-hemispheric ischemic or hemorrhagic *stroke* in the territory of the middle cerebral artery, with about half of the patients suffering from aphasia following a stroke in this region [28]. Symptomatology normally depends on the lesion size, location, or both. For example, speech perception deficits typically arise from highly localized damage in Heschl's gyrus and their severity correlates with the lesion extent, while broader language-related deficits (such as naming impairments) may originate from damage in diverse regions and are mostly dependent upon lesion size [29]. An important exception relates to the existence of a white-matter bottleneck lying deep within the frontal lobe: Even very small lesions in this area, representing the convergence point between several major connecting fiber tracts within the language network (i.e., uncinate fasciculus, inferior fronto-occipital fasciculus, anterior thalamic radiations), result in semantic deficits across modalities [26].

Focal lesions in left-hemispheric language regions cause significant changes in normal brain physiology: Starting from early post-stroke stages, increased slow activity in the delta and theta range has been reliably observed with EEG and MEG [7, 14, 30–33]; similarly, activity in the beta range—indexing cortical arousal and input processing—is typically decreased in chronic aphasic patients performing linguistic tasks [4, 34]. However, how does the system return to its normal functions? In general, functional restoration correlates with an increase in alpha-band phase synchronization [35]. More specifically, two main plasticity mechanisms have been described to account for functional recovery after brain damage. They rely on a takeover of a lost function either by i) homologous regions in the right hemisphere or ii) perilesional areas in the left hemisphere. Concerning the former, white matter integrity seems to be responsible, at least in some cases, for the compensatory role assumed by right-hemispheric homologs. In a recent study, Piai and colleagues [10] used a multi-modal approach to investigate the correlation between physiological compensation after left-hemispheric stroke and the integrity of white matter tracts connecting the temporal poles bilaterally. Over the course of a picture naming task, the authors observed a decrease in alpha-beta power which was left lateralized in healthy participants but right lateralized in patients with left-hemispheric stroke and intact posterior callosal fibers. Similarly, Rosso and colleagues [36] investigated picture naming in a sample of aphasic patients with damage in left IFG. Combining tDCS and functional connectivity, the authors observed improved picture naming after cathodal stimulation of the right homolog of Broca's area only in patients with an intact arcuate fasciculus. Taken together, this evidence suggests that the structural integrity of language hubs and connections may be

critical for the recruitment of spared functional regions [37]. However, whether the takeover by right homolog areas may be adaptive or maladaptive is still a matter of dispute. For example, in stroke patients, synchronization between spontaneous alpha oscillations originating from the IFG and other brain regions correlates positively with verbal fluency measures when measured in the left hemisphere, but negatively when measured in the right IFG [7]. It is possible that the right-hemispheric takeover may be necessary or at least helpful in initial stages, while the left-hemispheric perilesional regions need to recover; ultimately, however, better outcomes are associated with a restoration of the normal functional activity to the left side [38]. A recent MEG study [39] demonstrated an increase in left-hemispheric magnetic mismatch negativity (mMMN) responses to auditorily presented words following speech therapy, indicating functional recovery. Similarly, Campana and colleagues [6] used a combined LSM and tDCS approach to investigate picture naming improvement in aphasic patients. The authors used tDCS to stimulate areas surrounding lesions in the left hemisphere and they observed that—while this treatment benefitted all patients—those with greater integrity of cortical language hubs (IFG, insula, operculum, inferior parietal cortex, *see* Subheading 4) had the best outcomes. Preservation of subcortical regions, including white matter tracts connecting anterior and posterior areas (superior and inferior longitudinal fasciculus) and the basal ganglia, is equally important in predicting recovery; in particular, it has been suggested that the left basal ganglia might inhibit dysfunctional cortical activity, thus facilitating functional reorganization in the spared cortex [6, 40].

Besides stroke, language and speech impairments may arise as a consequence of localized traumatic brain injury (TBI) often resulting in subdural and epidural hematomas, intraparenchymal hematomas, and contusions [41]. The injury itself derives from the impact of an external force either penetrating the skull (open-head injuries) or causing a blow to the head without breaking the skull (closed-head injuries).[1] These lesions typically result in mild and transient language deficits whose severity depends upon the location and severity of impact on the skull: While cognitive functioning usually returns to baseline 1–3 months after mild injuries, long-term sequelae may persist and become chronic after 2 years post-injury in more severe cases [42, 43]. Language impairments in TBI are often classified as secondary to a primary impairment of executive functions or as affecting aspects of language such as

[1] It is important to note that in most cases, traumatic brain injuries entail a combination of a focal lesion (the contact point with the skull or with an external object) and a diffuse lesion (often due to the shearing and tearing of white matter tracts, for example in the case of car accidents). A distinction between the two components can be made only on an individual basis. *See* also [22, 41].

pragmatics [44]. Interestingly, however, other studies challenge this claim by suggesting that subtle deficits (lexical-semantic processing [45, 46]; syntactic processing [47]) may simply go unnoticed in behavioral tasks, but can emerge with more sophisticated electrophysiological measurements due to their enhanced sensitivity. For example, even with comparable behavioral performance, TBI patients show signs of abnormal language processing, as evidenced by a lack of a P600 component—a positive event-related response (ERP) typically peaking around 600 ms after stimulus presentation and associated with the processing of syntactic and grammatical incongruences [48]—in response to the detection of syntactic abnormalities [49] (*see* also [47]).

2.2 Pathologies Due to Diffuse Damage

Diffuse brain damage is caused by widely distributed damage to axons, diffuse vascular injury, hypoxic-ischemic injury, brain swelling (or edema [41]), and neurodegenerative diseases (e.g., primary progressive aphasia (PPA) [50, 51]). Diffuse axonal injury (DAI [52]) is especially frequent after TBI related to vehicle accidents, falls, or sports activity (e.g., [53]). These types of collision entail a rapid acceleration-deceleration movement of the head resulting in a typical pattern of damage, characterized by (i) a compression of the brain at the site of the impact (called *coup*), (ii) a second bruise on the opposite side (*contrecoup*), and (iii) DAI due to the shearing and tearing of axons either sagitally or laterally, with the latter direction being associated with more severe deficits [22, 41, 52]. Diffusion tensor imaging (DTI [54–57]) may uncover these latter white matter damages, which are otherwise typically elusive in routine instrumental analyses partially because of extreme individual variability [54, 58].

A major consequence of DAI is that the balance between cortical and subcortical regions may be disrupted, thus causing disconnection syndromes characterized by relatively frequent[2] and highly persistent language deficits [45]. However, the subtlety of the deficits (among others: verbal associations, sentence construction, synonym generation, comprehension of ambiguous sentences, temporal structure comprehension, naming) often escapes standard neuropsychological assessments [44, 59–62]. As a consequence, even in this case, language deficits (when recognized) are frequently considered secondary to a more general impairment in executive functions. Nonetheless, recent studies targeting language abilities in TBI patients identified semantic abilities as a main area of concern (e.g., [2]). For example, several studies noted a predominant semantic deficit following diffuse damage by targeting the N400 component, a negative ERP response typically peaking

[2] Subtle deficits are especially frequent following mild TBI, as—in severe injuries—they may be masked by more global deficits (e.g., coma, motor deficits [22]). A full description of the different forms and severity grades of TBI is, however, outside the scope of this chapter (but *see*, e.g., [59]).

around 400 milliseconds after stimulus presentation and indexing word retrieval or access to semantic memory [63]. More specifically, these studies found that the N400 response to semantic priming was either delayed, reduced, or even absent in TBI patients as compared to healthy controls even when the experiment was conducted several years post-injury [1, 3, 22].

Neurodegenerative diseases represent another source of diffuse brain pathology causing language and speech deficit symptoms [64]. Neurodegeneration may either primarily affect cortical regions, as evident in progressive semantic dementia (SD [26, 64]) and PPA [50, 51], or disrupt the normal functioning of subcortical structures such as the basal ganglia in Parkinson's disease (PD; e.g., [65]). Electrophysiological findings across neurodegenerative pathologies typically reveal signs of widespread neurophysiological deficits, including loss of alpha rhythm and generalized EEG slowing with an excess of theta rhythm (e.g., [66]). Similarly to DAI, neurodegeneration is also frequently accompanied by semantics-related deficits [67]; for example, the N400 effect already mentioned for diffuse TBI is also a marker of semantic deficits in Alzheimer's disease (AD) and is associated with an increase conversion risk from mild cognitive impairment to AD [68]. On the other hand, semantic deficits observed in diffuse pathologies differ from those reported in focal damage: In dementias and diffuse brain pathologies in general, semantic deficits are precipitated by the loss of stored semantic representations caused by neuronal death, while in focal damage information may still be available (i.e., neurons are not lost) but difficult to access [64]. As partially common underlying mechanisms in the altered neurophysiology and symptomatology of diffuse pathologies may exist, specific markers are difficult to identify: A paradigmatic example is semantic dementia, a variant of frontotemporal dementia (FTD), which is characterized by damage to the anterior temporal lobe and extensive semantic deficits often at the single word level [67, 69–73]. While older studies and clinical guidelines reported typically normal resting state cortical activity in SD (e.g., [66, 74]; *see* also [75, 76]), recent evidence, employing more fine-grained methods of analysis, challenges this conclusion. Particularly promising in this regard is the analysis of microstate topography of resting state EEG: In this approach, a multichannel electrode array is scanned to identify topographies of electric potentials that remain stable for c.a. 100 ms before transitioning into a different state [77]. These quasi-stable topographies (or "microstates") are assumed to reflect the activity of different neural populations coding for distinct cognitive processes. By employing this method, Grieder and colleagues [74] revealed significant differences between SD and both AD patients and healthy controls in at least two microstate classes. More recent studies further confirmed this first counterevidence to the long-standing claim of a non-pathological resting state EEG

in SD. For example, different electrophysiological signatures across neurodegenerative forms were observed in a connectivity-based MEG study, in which distinct connectivity profiles—defined by distribution and frequency of oscillatory activity—were found to distinguish between AD and several variants of FTD [76].

While the neurodegenerative forms described so far predominantly relate to cortical gray matter, other pathologies are characterized by subcortical damage: Parkinson's disease is a paradigmatic example of a neurodegenerative process primarily affecting the basal ganglia and resulting in both semantic and syntactic deficits ([65, 78] *see* following paragraph).

2.3 Disorders of Perception Versus Production

Language-related pathologies may be distinguished as receptive or productive, depending on whether they primarily affect language input (i.e., comprehension) or output (i.e., production). The most paradigmatic example of the former class is represented by Wernicke's aphasia, a prototype of the so-called fluent aphasic syndromes, characterized by fluent speech in the presence of impairments in speech comprehension and word repetition. Productive aphasias—such as Broca's aphasia—often are non-fluent, in the sense that the speech output is severely reduced and characterized by syntactic deficits, agrammatism, anomia, and dysprosody. To this day, aphasia classification rests on the Wernicke-Lichtheim model, an early lesion model linking brain damage location with function. According to this model, damage to the language "motor center"—Broca's area—would cause typical symptoms of a non-fluent aphasic syndrome, while damage to the "sensory center"—Wernicke's area—would result in fluent aphasia, and a lesion interrupting the connection between these hubs would cause a conduction aphasia [24, 79–81].[3]

This "classical" model has the advantage of being simple, intuitive, and applicable in clinical practice; however, many researchers consider it obsolete and inadequate in light of current advances in neuro-anatomical knowledge [85–88]. Particularly problematic is the exclusive focus on cortical hubs and the exclusion of subcortical nuclei that have been consistently implicated in both language perception and production [19, 89] and whose lesion often results in aphasic symptoms [90, 91]. For example, several functional and metabolic (positron emission tomography—PET) studies in healthy adults report activity in the left striatal complex during syntactic [92, 93], as well as semantic processing (e.g., [94–96]). This evidence has been further refined by studies on clinical populations characterized by striatal degeneration (e.g., PD or Huntington's disease [97, 98]) showing that parts of the basal ganglia

[3] Here, the model is simplified to focus on perceptive and productive deficits; originally, it includes a third "concept" center and its connections to the motor and sensory hubs [82–84].

system may be actively engaged during language reception at different processing levels [20, 89, 99]. For example, PD patients typically encounter difficulties in sentence comprehension, although it is unclear whether this relates to a pure syntactic deficit, a slowing in processing speed (e.g., [100]), or a more generalized timing deficit [21, 65, 101].

In addition to receptive deficits, Parkinson's disease patients often suffer from severe motor impairments, extending to productive speech disorders—including phonation, articulation, and prosody [102]. At the neurophysiological level, these deficits are reflected by altered brain activity on several accounts. For example, a recent study by Sörös and colleagues in medicated PD patients (i.e., under dopaminergic treatment) uncovered an increase in oscillatory brain activity in the β-band during the preparation for visually cued overt speech, in stark contrast with the typical decrease observed for speech preparation in healthy individuals and for limb movement in PD patients [103]. While the exact causes of this phenomenon are still unclear, it has been hypothesized that excessive β-band oscillations may arise as a consequence of chronic dopamine depletion to the subthalamic nucleus (STN [104]; *see* Subheading 3).

2.4 Developmental Language Disorders

The acquisition of language is one of the most significant and consequently most anticipated landmarks in a child's development. Despite the complex nature of the underlying processes, the acquisition of language skills is typically achieved astonishingly quickly and effortlessly. Nevertheless, every level of the interplay of genetic, physiological, and psychological factors in these processes is susceptible to aberrations that manifest in a wide range of developmental language disorders. Median prevalence estimates for speech and language delay provide figures close to 6% for the normal population [105]. However, such estimates are complicated by heterogeneous yet overlapping phenotypes and comorbidity with global developmental conditions such as autism spectrum disorder, learning disability, or hearing impairments [106, 107]. For most developmental language disorders, no clear cause can be identified, although mutations in the FOXP2 gene that cause heritable developmental verbal dyspraxia establish a strong case for genetic factors [108, 109].

The most common language disorder in children affects receptive and/or expressive abilities despite normal non-verbal intellectual abilities. Different terms and sub-classifications have been used to describe this phenomenon, most prominently as *Specific Language Impairment* (SLI) or, less commonly but more recently, as Developmental Language Disorder (DLD [110, 111]). SLI is characterized by a delayed onset and protracted development of language skills between 3 and 5 years of age, with an overall prevalence of about 7.4% [112, 113]. Electrophysiological research

in this context takes advantage of the excellent temporal resolution of EEG to delineate functional characteristics of SLI along the time course of sensory and language processing. Previous studies have focused on early (peak amplitude latencies shorter than about 300 ms) and later ERP components of the EEG. Differences between typically developing and children with SLI in the timing and peak amplitudes of early components such as the N100 and mismatch negativity suggest atypical sensory information processing, whereas atypical ERP morphology and hemispheric lateralization in later components suggest also atypical attention-dependent information processing in SLI, despite a considerable amount of heterogeneity in the respective results [114]. Recent research provides further evidence along these lines, while it also highlights some of the inconsistencies resulting from the ERP approach. For example, preschoolers with SLI showed a delayed time course and more diffuse scalp topography of the N400 effect at the sentence level but not of earlier sensory responses such as the N1/P2 complex [115]. Although such findings may be taken as supportive of the notion of a language specific impairment, the results of studies employing both verbal and non-verbal visual "oddball" paradigms focusing on P3/P3b ERP components suggest higher processing costs in SLI children across cognitive domains [116].

Stuttering is another developmental language disorder with a high prevalence. Like SLI, stuttering is a phenomenon with still mostly unclear causes, despite evidence for strong genetic factors [117]. Stuttering is characterized by repetitions, prolongations, and blocking of speech sound articulation. Life-span prevalence rates vary but are probably close to 0.75%, with considerably higher rates in children under 6 years of age [117]. EEG studies of children who stutter confirm verbal and non-verbal processing dysfunctions [118]. Results from non-verbal auditory oddball paradigms comparing pre-school children who stutter with non-stuttering controls did not yield group differences in early P1/N1 ERP components but confirmed a significant P3 only in controls, suggesting less robust allocation of attention and working memory updating [119]. Children who stutter also showed a reduced P3 as opposed to an excessive N2 in a visual Go/No-go task [120]. Considering the overall high rate of natural recovery [117], it is important to note that subtle differences in ERP markers of semantic processing (N400, late positive component) may be predictors of stuttering persistence [121]. Such findings confirm a unique role and sensitivity of verbal and non-verbal EEG/ERP paradigms, which should complement a holistic neuropsychological approach to developmental language disorders [111].

3 Role of Subcortical Structures in Language Processing

Language is a complex, yet highly automated system entailing several subcomponents. While the role of cortical structures in language processing has been well investigated using lesion and/or neuroimaging approaches (M/EEG, functional Magnetic Resonance Imaging-fMRI, and PET), the role of subcortical structures is less explored, potentially due to contradictory results. Often subcortical aphasia does not lead to persistent symptoms and language deficits [90, 91, 122] or primarily coincides with speech production deficits that are more motoric in nature. For example, the phenomenon of palilalia, realized by arbitrary repetitions of syllables, words, and word combinations, may be produced with increasing speed during speech production in PD patients. However, this phenomenon results from a motor planning deficit rather than a speech production deficit per se. Similarly, Wallesch and Blanken [123] suggest that speech automatisms in PD are linked to a pre-articulatory deficit based on the reduced capacity to inhibit irrelevant target expressions. While production deficits (primarily prosodic) have been reported in PD patients, it has been argued that linguistic processes such as phonology, lexical semantics, and syntax in language perception are not affected. Rather, these processes may appear deficient, but may be secondary to attentional and/or working memory deficits. Often these deficits mimic frontal cortical phenomena such as verbal working memory or verbal fluency deficits [124]. In an early information-processing model, Wallesch and colleagues [125, 126] proposed that a cortico-striato-pallido-thalamo-cortical loop regulates response preparation and response selection. According to this model, multiple lexical alternatives (i.e., response alternatives) are produced and released in the posterior perisylvian cortex, then carried to the anterior perisylvian cortex and the striatum in parallel modules. Thus, the striatum may monitor various types of lexical alternatives (situational, emotional, motivational, and semantic) and play an immanent role in the selection of a contextually appropriate lexical candidate. Structurally, the model can be criticized as basal ganglia lesions often include white matter lesions and thus are not exclusive.

Next to the striatum, the thalamus has been discussed as the subcortical structure that may be engaged in language processing. Lesions of specific thalamic nuclei can impair speech production, word finding, and cause paraphasia. For example, speech production impairments in PD have been attributed to a degenerative process affecting the STN as a consequence of chronic dopaminergic depletion [104, 127]. This hypothesis aligns with and updates a classical model of subcortical speech production firstly proposed by Crosson [128] and supported by thalamic lesion data (e.g., [129–131]). In this model, the thalamus, along with the basal ganglia,

engages in the selection of produced speech segments in a striato-thalamo-cortical network modulated by the frontal cortex [132]. Wallesch [124] described three anatomical models that assign a potential role to the thalamus during language processing (*see* also [132]). First, the ventral thalamic nuclei VA and VL are part of the cortico-striato-pallido-thalamo-cortical loop that regulates speech production. Second, the pulvinar as the largest thalamic nucleus projects mainly to the posterior temporal language cortex. Third, lesions of non-specific thalamic nuclei can disrupt the connection between the ascending reticular activation system (cerebellum) and the cortex, resulting in attentional, motivational, and consciousness deficits that may supersede language deficits. According to these proposed models, the striatum and the thalamus are plausible structures regulating language processing. Language deficits may therefore be an epiphenomenon of attentional and/or working memory deficits.

Finally, it remains to be unambiguously established whether language production and comprehension deficits attributed to basal ganglia lesions may be caused by lesions in other regions that are either adjacent to or connected with these nuclei. For example, aphasia resulting from a left-hemispheric basal ganglia lesion may also derive from pathway lesions that in turn cause cortical deficits within the same hemisphere [132]. Weiller and colleagues [133] pointed out that large striatal lesions could also include cortical insula lesions that affect the blood supply system of the middle cerebral artery, resulting in aphasia.

To extend the potential multifunctional role of the basal ganglia in language processing, there has been a recent revival in investigating their linguistic and non-linguistic functions. As described above, there have been early reports on prosodic production deficits primarily after putaminal lesions. A note of caution needs to be raised as to whether such prosodic deficits are motoric in nature or actually reflect a deficit in realizing basic acoustic properties of prosody such as fundamental frequency, duration, and intensity. This, of course, also applies to the perception of prosody. PD has been proposed as a model to understand how the basal ganglia contribute to the processing of linguistic or non-linguistic prosodic tone.

In the past decades, a number of laboratories published neuroimaging and lesion evidence that describes a highly distributed network involving both cortical and subcortical structures during the perception of emotional tone (e.g., [134–137]). However, not all of the imaging studies reported activation of the basal ganglia [136], and the contribution of the basal ganglia in decoding prosodic cues has often been reported as secondary to cortical deficits or to impairments in decoding the finer temporal suprasegmental structure of auditory input [138]. Still, some neuropsychological studies have reported discrimination and recognition deficits of

emotional prosody after focal basal ganglia lesions [139–141]. In a series of studies, Pell and Leonard [141–143] systematically investigated the perception of emotional prosody utilizing discrimination, identification, and emotional feature rating tasks in PD patients and age-matched controls. In comparison to controls, PD patients showed an overall reduction in the perception of emotional prosodic cues. The authors took these results as evidence that the basal ganglia play a regulatory role in "predicting the value of cue sequences within a temporal sensory event" (*see* also [138] for an elaborative standpoint on this view). In conclusion, non-linguistic and linguistic prosodic processing seems to be modulated by the basal ganglia. However, in comparison to grammatical and lexical-semantic processing, the present evidence seems to point to a non-domain-specific function of the basal ganglia in these processes, a role involving the temporal encoding of linguistic or non-linguistic cues in an auditory sequence.

4 Cortico-Subcortical Networks Involved in Language Pathologies

Starting from the pivotal studies of Broca and Wernicke, lesion methods have been the gold standard to investigate brain regions involved in language perception and production. Due to the development of non-invasive methods (e.g., fMRI, DTI, M/EEG, TMS), this perspective has been progressively broadened to embrace a model of the language brain as a connectome [18, 88]. More specifically, the language system shows properties of a "large-scale distributed neural network" entailing critical hubs, which are necessary for a given function, and supporting nodes, interconnected with each other [11, 12]. Many excellent articles are available describing the language network and its components in detail in relation to several aspects of language (e.g., [144–148] *see* [149] for an evolutionary perspective). In short, in the adult brain the language network is thought to encompass a left-lateralized set of regions surrounding the Sylvian fissure and mostly located in the frontal, parietal, and temporal lobe, and their connections ([150]; *see* [151] for a developmental angle). It is assumed that these regions are organized along two main systems, a ventral pathway and a dorsal pathway [145, 147]. The ventral pathway deals with the mapping of speech sounds to meaning. Anatomically, it comprises connections between the IFG and the temporal poles—via the uncinate fasciculus—and with the occipital lobe—via the inferior fronto-occipital fasciculus. The dorsal pathway, on the other hand, is involved in speech production, segmentation, and syntactic processing; anatomically, it connects Wernicke's territory (temporo-parietal cortex) with (i) the inferior parietal cortex and ultimately the premotor cortex via the superior longitudinal fasciculus and (ii) Broca's area, thanks to the arcuate fasciculus

[144, 145]. Further, the role of basal ganglia (e.g., subthalamic nucleus, caudate), thalamus, and cerebellum cannot be overlooked [19, 152], particularly regarding speech: Acting in concert with motor cortical regions (pre/SMA, pre/motor cortex), these subcortical areas facilitate both speech perception and production [20].

How and under which premise does this complex and multilayered language network reorganize as a consequence of brain damage [148]? Given the interconnection between main hubs and ancillary cortico-subcortical regions, even small local damage may cause neurophysiological changes in distant regions due to diaschisis [13], large-scale effects due to lesioned connections [26], or even global updates in normal neurophysiological patterns (e.g., by increasing the amount of slow delta waves; [7, 14, 30, 31]. How exactly these plastic changes come to be is still a matter of debate, and largely depends on whether hubs, ancillary nodes, or connections are primarily damaged. As different pathologies are likely to target different nodes or connections in the language network, they could inform on plastic changes occurring in distinct parts of the system. For example, semantic deficits rarely arise as a consequence of cerebrovascular accidents [12], but these are frequently observed in neurodegenerative processes, such as those causing PPA. By studying this pathology, it was discovered that resting state EEG/MEG activity is characterized by an increase in slow theta and delta frequencies [8, 153]; however, when neurodegeneration spreads from motor regions— supplementary motor cortex—it gives rise to speech deficits (i.e., apraxia of speech) in the absence of pathological signs in the EEG signal [153]. Thus, the plastic reorganization depends, among other things, on the region being affected first in the disease progression.

5 Novel Therapeutic Approaches

Language pathologies and disorders, whatever their cause, come at a great individual and societal cost. For these reasons, much research is dedicated to treatments to help ameliorate the patients' life quality. This effort is particularly important for highly invalidating pathologies with a high prevalence, such as post-stroke aphasia. While behavioral speech therapy remains the norm in the treatment of subacute and chronic aphasia, non-invasive brain stimulation techniques, such as TMS and tDCS, have been increasingly applied as a complementary approach with promising results [148, 154–156]. TMS and tDCS are hypothesized to improve language abilities by facilitating the recovery of left-hemispheric perilesional regions either by inhibiting right-hemispheric homologs (e.g., [157]) or by stimulating left-hemispheric perilesional regions (e.g., [6]). However, the long-term efficacy of these effects—

especially in the case of tDCS—remains to be further investigated [148]. More recently, the positive results of non-invasive stimulation in post-stroke aphasia inspired the application of such methods in neurodegenerative diseases, such as PPA [158] and PD [159, 160]. While non-invasive stimulation in PD has primarily targeted motor symptoms (e.g., [161]), language impairments have been the focus of TMS and TDCS applications in PPA. The few studies conducted so far in PPA cautiously report improvement in semantic processing (e.g., [162, 163]) correlating with a decrease in aberrant functional connectivity between language network regions [164]. While further research is warranted, the initial encouraging steps may suggest future venues and directions to improve life quality even in neurodegenerative patients.

Concerning developmental language disorders, therapeutic interventions apply a wide range of methods, although approaches strictly focusing on grammatical aspects of language have become less dominant. A potential unifying framework for the description of pathologies and the development of alternative treatments is the Atypical Rhythm Risk Hypothesis, which suggests that individually different and atypical rhythm processing abilities factor into the profile of developmental speech and language disorders, including stuttering [165]. Atypical rhythm processing abilities may in turn reflect patterns of inefficient or inconsistent neural oscillatory activity during speech processing. Interventions specifically targeted at training these abilities and/or at modulating the underlying neural mechanisms, for example, by means of neurostimulation, may therefore provide a promising starting point for the development of assessment and intervention strategies that incorporate electrophysiological components.

6 Summary and Future Directions

In this chapter, we summarized evidence on the impact of brain damage on the neurophysiology of the language network. Damage to both cortical and subcortical regions may result in language- and speech-related pathologies, although several factors contribute to the severity and outcome. For example, damages locally affecting the gray matter or basal ganglia typically result in more specific deficits than lesions affecting a long-range white matter bundle. In the latter cases, the injury, albeit localized, might interrupt the flow of information between distant regions, thus leading to a massive neurophysiological reorganization of the entire system. Yet another factor to be considered is the extent to which the system itself is plastic: Brain damage can be compensated particularly well in children within a specific window of brain plasticity (usually between 1 and 5 years of age) but may lead to significant chronic deficits afterward [166, 167]. We then focused on the

difference between perceptive and productive deficits; in doing so, we attempted to overcome classical cortical models of language organization by emphasizing the role of subcortical structures in linguistic pathologies.

Throughout this chapter, we stressed the idea that, whenever possible, a multi-modal approach is preferrable: The use of combined EEG and VBM/DTI in concert with LSM has proven effective to characterize not only the lesion, but the time course of recovery (e.g., *see* [10]). More importantly, the use of multimodal techniques sheds light on a view of the brain that is gaining new momentum: Most cognitive systems—including language—are not to be considered as encapsulated collections of distinct hubs; rather, they should be viewed as complex connectomes, in which the connections between regions are as important as the hubs and nodes themselves. How plasticity is implemented in such a complex dynamical system is a matter that will require additional research. Only by knowing mechanisms underlying functional recovery, it will be possible to develop new therapies and interventions. Besides the aforementioned non-invasive stimulation techniques, other promising candidates in this direction may be the use of stem cells to restore damaged tracts or the development of state-of-the-art prosthetics and robotic systems taking advantage of electrophysiological advancements in brain computer interfaces of TMS-based interventions [168].

7 Conclusion

This chapter focused on how normal neurophysiology is altered by brain damage. Electrophysiological methods as compared to other methods, such as fMRI, offer several advantages which are particularly relevant for clinical populations: Not only is electroencephalography typically cheaper than magnetic resonance imaging, but it is also portable and allows tracking for fine-grained temporal aspects both within task and in the recovery process. Hence, identifying pathology-specific markers of brain damage and recovery may allow for a quicker establishment of perspective treatments at the patient's bedside, thus maximizing the chances of therapeutic success.

References

1. Knuepffer C et al (2012) Reduced N400 semantic priming effects in adult survivors of paediatric and adolescent traumatic brain injury. Brain Lang 123:52–63. https://doi.org/10.1016/j.bandl.2012.06.009
2. Fratantoni JM et al (2017) Electrophysiological correlates of word retrieval in traumatic brain injury. J Neurotrauma 34:1017–1021. https://doi.org/10.1089/neu.2016.4651
3. Münte TF, Heinze H-J (1994) Brain potentials reveal deficits of language processing after closed head injury. Arch Neurol 51:482–493. https://doi.org/10.1001/archneur.1994.00540170058017

4. Kielar A, Deschamps T, Jokel R, Meltzer JA (2016) Functional reorganization of language networks for semantics and syntax in chronic stroke: evidence from MEG. Hum Brain Mapp 37:2869–2893. https://doi.org/10.1002/hbm.23212
5. Kielar A et al (2018) Abnormal language-related oscillatory responses in primary progressive aphasia. Neuroimage Clin 18:560–574. https://doi.org/10.1016/j.nicl.2018.02.028
6. Campana S, Caltagirone C, Marangolo P (2015) Combining voxel-based lesion-symptom mapping (VLSM) with A-tDCS language treatment: predicting outcome of recovery in nonfluent chronic aphasia. Brain Stimul 8:769–776. https://doi.org/10.1016/j.brs.2015.01.413
7. Dubovik S et al (2012) The behavioral significance of coherent resting-state oscillations after stroke. NeuroImage 61:249–257. https://doi.org/10.1016/j.neuroimage.2012.03.024
8. Kielar A et al (2019) Slowing is slowing: delayed neural responses to words are linked to abnormally slow resting state activity in primary progressive aphasia. Neuropsychologia 129:331–347. https://doi.org/10.1016/j.neuropsychologia.2019.04.007
9. Reid LB et al (2015) Interpreting intervention induced neuroplasticity with fMRI: the case for multimodal imaging strategies. Neural Plast 2016:e2643491. https://doi.org/10.1155/2016/2643491
10. Piai V et al (2017) Neuroplasticity of language in left-hemisphere stroke: evidence linking subsecond electrophysiology and structural connections. Hum Brain Mapp 38:3151–3162. https://doi.org/10.1002/hbm.23581
11. Mesulam M-M (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 28:597–613. https://doi.org/10.1002/ana.410280502
12. Mesulam M-M et al (2014) Primary progressive aphasia and the evolving neurology of the language network. Nat Rev Neurol 10:554–569. https://doi.org/10.1038/nrneurol.2014.159
13. Carrera E, Tononi G (2014) Diaschisis: past, present, future. Brain 137:2408–2422. https://doi.org/10.1093/brain/awu101
14. Spironelli C, Angrilli A (2009) EEG delta band as a marker of brain damage in aphasic patients after recovery of language. Neuropsychologia 47:988–994. https://doi.org/10.1016/j.neuropsychologia.2008.10.019
15. Catani M, Mesulam M (2008) What is a disconnection syndrome? Cortex 44:911–913. https://doi.org/10.1016/j.cortex.2008.05.001
16. Dick AS, Bernal B, Tremblay P (2014) The language connectome: new pathways, new concepts. Neuroscientist 20:453–467. https://doi.org/10.1177/1073858413513502
17. Friederici AD (2011) The brain basis of language processing: from structure to function. Physiol Rev 91:1357–1392. https://doi.org/10.1152/physrev.00006.2011
18. Friederici AD, Gierhan SME (2013) The language network. Curr Opin Neurobiol 23:250–254. https://doi.org/10.1016/j.conb.2012.10.002
19. Eisinger RS et al (2018) Non-motor characterization of the basal ganglia: evidence from human and non-human primate electrophysiology. Front Neurosci 12:385. https://doi.org/10.3389/fnins.2018.00385
20. Kotz SA, Schwartze M (2010) Cortical speech processing unplugged: a timely subcortico-cortical framework. Trends Cogn Sci 14:392–399. https://doi.org/10.1016/j.tics.2010.06.005
21. Kotz SA, Schwartze M, Schmidt-Kassow M (2009) Non-motor basal ganglia functions: a review and proposal for a model of sensory predictability in auditory language perception. Cortex 45:982–990. https://doi.org/10.1016/j.cortex.2009.02.010
22. Gaetz M (2004) The neurophysiology of brain injury. Clin Neurophysiol 115:4–18. https://doi.org/10.1016/s1388-2457(03)00258-x
23. Broca P (1865) Sur le siège de la faculté du langage articulé. Bull Mem Soc Anthropol Paris 6:377–393
24. Wernicke C (1974) Der aphasische Symptomencomplex: eine psychologische Studie auf anatomischer Basis. Springer, Berlin, Heidelberg
25. Bates E et al (2003) Voxel-based lesion–symptom mapping. Nat Neurosci 6:448–450. https://doi.org/10.1038/nn1050
26. Mirman D et al (2015) Neural organization of spoken language revealed by lesion–symptom mapping. Nat Commun 6:6762. https://doi.org/10.1038/ncomms7762
27. Mirman D, Thye M (2018) Uncovering the neuroanatomy of core language systems using lesion-symptom mapping. Curr Dir Psychol Sci 27:455–461. https://doi.org/10.1177/0963721418787486

28. Boehme AK et al (2016) Effect of aphasia on acute stroke outcomes. Neurology 87:2348–2354. https://doi.org/10.1212/WNL.0000000000003297
29. Thye M, Mirman D (2018) Relative contributions of lesion location and lesion size to predictions of varied language deficits in post-stroke aphasia. Neuroimage Clin 20:1129–1138. https://doi.org/10.1016/j.nicl.2018.10.017
30. Meinzer M et al (2004) Intensive language training enhances brain plasticity in chronic aphasia. BMC Biol 2:20. https://doi.org/10.1186/1741-7007-2-20
31. Nicolo P et al (2015) Coherent neural oscillations predict future motor and language improvement after stroke. Brain 138:3048–3060. https://doi.org/10.1093/brain/awv200
32. Butz M et al (2004) Perilesional pathological oscillatory activity in the magnetoencephalogram of patients with cortical brain lesions. Neurosci Lett 355:93–96. https://doi.org/10.1016/j.neulet.2003.10.065
33. Vieth JB, Kober H, Grummich P (1996) Sources of spontaneous slow waves associated with brain lesions, localized by using the MEG. Brain Topogr 8:215–221. https://doi.org/10.1007/BF01184772
34. Spironelli C, Manfredi M, Angrilli A (2013) Beta EEG band: a measure of functional brain damage and language reorganization in aphasic patients after recovery. Cortex 49:2650–2660. https://doi.org/10.1016/j.cortex.2013.05.003
35. Westlake KP et al (2012) Resting state alpha-band functional connectivity and recovery after stroke. Exp Neurol 237:160–169. https://doi.org/10.1016/j.expneurol.2012.06.020
36. Rosso C et al (2014) Broca's area damage is necessary but not sufficient to induce after-effects of cathodal tDCS on the unaffected hemisphere in post-stroke aphasia. Brain Stimul 7:627–635. https://doi.org/10.1016/j.brs.2014.06.004
37. Nagata K et al (1982) Topographic electroencephalographic study of cerebral infarction using computed mapping of the EEG. J Cereb Blood Flow Metab 2:79–88. https://doi.org/10.1038/jcbfm.1982.9
38. Crosson B et al (2007) Functional MRI of language in aphasia: a review of the literature and the methodological challenges. Neuropsychol Rev 17:157–177. https://doi.org/10.1007/s11065-007-9024-z
39. Mohr B et al (2016) Hemispheric contributions to language reorganisation: an MEG study of neuroplasticity in chronic post stroke aphasia. Neuropsychologia 93:413–424. https://doi.org/10.1016/j.neuropsychologia.2016.04.006
40. Parkinson RB et al (2009) Lesion characteristics related to treatment improvement in object and action naming for patients with chronic aphasia. Brain Lang 110:61–70. https://doi.org/10.1016/j.bandl.2009.05.005
41. Andriessen TM, Jacobs B, Vos PE (2010) Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. J Cell Mol Med 14:2381–2392. https://doi.org/10.1111/j.1582-4934.2010.01164.x
42. Schretlen DJ, Shapiro AM (2003) A quantitative review of the effects of traumatic brain injury on cognitive functioning. Int Rev Psychiatry 15:341–349. https://doi.org/10.1080/09540260310001606728
43. Shenton ME et al (2012) A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. Brain Imaging Behav 6:137–192. https://doi.org/10.1007/s11682-012-9156-5
44. Mcdonald S (1992) Communication disorders following closed head injury: new approaches to assessment and rehabilitation. Brain Inj 6:283–292. https://doi.org/10.3109/02699059209029670
45. Barwood CH, Murdoch BE (2013) Unravelling the influence of mild traumatic brain injury (MTBI) on cognitive-linguistic processing: a comparative group analysis. Brain Inj 27:671–676. https://doi.org/10.3109/02699052.2013.775500
46. Hinchliffe FJ, Murdoch BE, Chenery HJ (1998) Towards a conceptualization of language and cognitive impairment in closed-head injury: use of clinical measures. Brain Inj 12:109–132. https://doi.org/10.1080/026990598122746
47. Butler-Hinz S, Caplan D, Waters G (1990) Characteristics of syntactic comprehension deficits following closed head injury versus left cerebrovascular accident. J Speech Lang Hear Res 33:269–280. https://doi.org/10.1044/jshr.3302.269
48. Coulson S, King JW, Kutas M (1998) Expect the unexpected: event-related brain response to morphosyntactic violations. Lang Cogn Process 13:21–58. https://doi.org/10.1080/016909698386582

49. Key-DeLyria Sarah E et al (2016) Sentence processing in traumatic brain injury: evidence from the P600. J Speech Lang Hear Res 59: 759–771. https://doi.org/10.1044/2016_JSLHR-L-15-0104
50. Gorno-Tempini ML et al (2011) Classification of primary progressive aphasia and its variants. Neurology 76:1006–1014. https://doi.org/10.1212/WNL.0b013e31821103e6
51. Mesulam M-M (2001) Primary progressive aphasia. Ann Neurol 49:425–432. https://doi.org/10.1002/ana.91
52. Adams JH et al (1989) Diffuse axonal injury in head injury: definition, diagnosis and grading. Histopathology 15:49–59. https://doi.org/10.1111/j.1365-2559.1989.tb03040.x
53. Ledwidge P (2018) The impact of sports-related concussions on the language system: a case for event-related brain potentials. Ann Behav Neurosci 1:36–46
54. Eierud C et al (2014) Neuroimaging after mild traumatic brain injury: review and meta-analysis. Neuroimage Clin 4:283–294. https://doi.org/10.1016/j.nicl.2013.12.009
55. Inglese M et al (2005) Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. J Neurosurg 103:298–303. https://doi.org/10.3171/jns.2005.103.2.0298
56. Irimia A et al (2012) Neuroimaging of structural pathology and connectomics in traumatic brain injury: toward personalized outcome prediction. Neuroimage Clin 1:1–17. https://doi.org/10.1016/j.nicl.2012.08.002
57. Ptak T et al (2003) Cerebral fractional anisotropy score in trauma patients: a new indicator of white matter injury after trauma. Am J Roentgenol 181:1401–1407. https://doi.org/10.2214/ajr.181.5.1811401
58. Ware JB et al (2017) Inter-subject variability of axonal injury in diffuse traumatic brain injury. J Neurotrauma 34:2243–2253. https://doi.org/10.1089/neu.2016.4817
59. Marini A, Zettin M, Galetto V (2014) Cognitive correlates of narrative impairment in moderate traumatic brain injury. Neuropsychologia 64:282–288. https://doi.org/10.1016/j.neuropsychologia.2014.09.042
60. Davis GA, Coelho CA (2004) Referential cohesion and logical coherence of narration after closed head injury. Brain Lang 89:508–523. https://doi.org/10.1016/j.bandl.2004.01.003
61. Ilie G, Cusimano MD, Li W (2017) Prosodic processing post traumatic brain injury – a systematic review. Syst Rev 6:1. https://doi.org/10.1186/s13643-016-0385-3
62. Wong MN, Murdoch B, Whelan B-M (2010) Language disorders subsequent to mild traumatic brain injury (MTBI): evidence from four cases. Aphasiology 24:1155–1169. https://doi.org/10.1080/02687030903168212
63. Lau EF, Phillips C, Poeppel D (2008) A cortical network for semantics: (de)constructing the N400. Nat Rev Neurosci 9:920–933. https://doi.org/10.1038/nrn2532
64. Mirman D, Britt AE (2014) What we talk about when we talk about access deficits. Philos Trans R Soc Lond B Biol Sci 369: 20120388. https://doi.org/10.1098/rstb.2012.0388
65. Kotz SA, Gunter TC (2015) Can rhythmic auditory cuing remediate language-related deficits in Parkinson's disease? Ann N Y Acad Sci 1337:62–68. https://doi.org/10.1111/nyas.12657
66. Chan D et al (2004) EEG abnormalities in frontotemporal lobar degeneration. Neurology 62:1628–1630. https://doi.org/10.1212/01.WNL.0000123103.89419.B7
67. Wilson SM (2017) Lesion-symptom mapping in the study of spoken language understanding. Lang Cogn Neurosci 32:891–899. https://doi.org/10.1080/23273798.2016.1248984
68. Olichney JM et al (2008) Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia. Neurology 70:1763–1770. https://doi.org/10.1212/01.wnl.0000281689.28759.ab
69. Neary D, Snowden J, Mann D (2005) Frontotemporal dementia. Lancet Neurol 4:771–780. https://doi.org/10.1016/S1474-4422(05)70223-4
70. Cope TE et al (2020) Anterior temporal lobe is necessary for efficient lateralised processing of spoken word identity. Cortex 126:107–118. https://doi.org/10.1016/j.cortex.2019.12.025
71. Hodges JR et al (1992) Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain J Neurol 115(Pt 6): 1783–1806. https://doi.org/10.1093/brain/115.6.1783
72. Ralph MAL et al (2017) The neural and computational bases of semantic cognition. Nat Rev Neurosci 18:42–55. https://doi.org/10.1038/nrn.2016.150

73. Ralph MAL et al (1998) Naming in semantic dementia—what matters? Neuropsychologia 36:775–784. https://doi.org/10.1016/S0028-3932(97)00169-3
74. Grieder M et al (2016) Discovering EEG resting state alterations of semantic dementia. Clin Neurophysiol 127:2175–2181. https://doi.org/10.1016/j.clinph.2016.01.025
75. Neary D et al (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51:1546–1554. https://doi.org/10.1212/WNL.51.6.1546
76. Sami S et al (2018) Neurophysiological signatures of Alzheimer's disease and frontotemporal lobar degeneration: pathology versus phenotype. Brain 141:2500–2510. https://doi.org/10.1093/brain/awy180
77. Khanna A, Pascual-Leone A, Michel CM, Farzan F (2015) Microstates in resting-state-EEG: current status and future directions. Neurosci Biobehav Rev 49:105–113. https://doi.org/10.1016/j.neubiorev.2014.12.010
78. Kotz SA et al (2003) Syntactic language processing: ERP lesion data on the role of the basal ganglia. J Int Neuropsychol Soc 9:1053–1060. https://doi.org/10.1017/S1355617703970093
79. Lichteim L (1885) On aphasia. Brain 7:433–484. https://doi.org/10.1093/brain/7.4.433
80. Tesak J, Code C (2008) Milestones in the history of aphasia: theories and protagonists. Psychology Press, London
81. Yourganov G, Smith KG, Fridriksson J, Rorden C (2015) Predicting aphasia type from brain damage measured with structural MRI. Cortex 73:203–215. https://doi.org/10.1016/j.cortex.2015.09.005
82. Geschwind N (1972) Language and the brain. Sci Am 226:76–83. https://doi.org/10.1038/scientificamerican0472-76
83. Geschwind N (1974) Conduction aphasia. In: Geschwind N (ed) Selected papers on language and the brain. Springer, Dordrecht, pp 509–529
84. Geschwind N (1970) The organization of language and the brain. Science 170:940–944
85. Anderson JM et al (1999) Conduction aphasia and the arcuate fasciculus: a reexamination of the Wernicke–Geschwind model. Brain Lang 70:1–12. https://doi.org/10.1006/BRLN.1999.2135
86. Binder JR (2017) Current controversies on Wernicke's area and its role in language. Curr Neurol Neurosci Rep 17:1–10. https://doi.org/10.1007/s11910-017-0764-8
87. Catani M, Jones DK, Ffytche DH (2005) Perisylvian language networks of the human brain. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc 57:8–16. https://doi.org/10.1002/ana.20319
88. Tremblay P, Dick AS (2016) Broca and Wernicke are dead, or moving past the classic model of language neurobiology. Brain Lang 162:60–71. https://doi.org/10.1016/j.bandl.2016.08.004
89. Booth JR et al (2007) The role of the basal ganglia and cerebellum in language processing. Brain Res 1133:136–144. https://doi.org/10.1016/J.BRAINRES.2006.11.074
90. Kang EK et al (2017) Subcortical aphasia after stroke. Ann Rehabil Med 41:725–733. https://doi.org/10.5535/arm.2017.41.5.725
91. Radanovic M, Mansur LL (2017) Aphasia in vascular lesions of the basal ganglia: a comprehensive review. Brain Lang 173:20–32. https://doi.org/10.1016/j.bandl.2017.05.003
92. Friederici AD et al (2003) The role of left inferior frontal and superior temporal cortex in sentence comprehension: localizing syntactic and semantic processes. Cereb Cortex 13:170–177. https://doi.org/10.1093/cercor/13.2.170
93. Moro A et al (2001) Syntax and the brain: disentangling grammar by selective anomalies. NeuroImage 13:110–118. https://doi.org/10.1006/nimg.2000.0668
94. Kotz SA et al (2002) Modulation of the lexical–semantic network by auditory semantic priming: an event-related functional MRI study. NeuroImage 17:1761–1772. https://doi.org/10.1006/nimg.2002.1316
95. Kuperberg GR et al (2000) Common and distinct neural substrates for pragmatic, semantic, and syntactic processing of spoken sentences: an fMRI study. J Cogn Neurosci 12:321–341. https://doi.org/10.1162/089892900562138
96. Ni W et al (2000) An event-related neuroimaging study distinguishing form and content in sentence processing. J Cogn Neurosci 12:120–133. https://doi.org/10.1162/089892900051137648
97. Longworth CE et al (2005) The basal ganglia and rule-governed language use: evidence from vascular and degenerative conditions. Brain 128:584–596. https://doi.org/10.1093/brain/awh387

98. Profant O et al (2017) Auditory dysfunction in patients with Huntington's disease. Clin Neurophysiol 128:1946–1953. https://doi.org/10.1016/j.clinph.2017.07.403
99. Hancock R, Richlan F, Hoeft F (2017) Possible roles for fronto-striatal circuits in reading disorder. Neurosci Biobehav Rev 72:243–260. https://doi.org/10.1016/j.neubiorev.2016.10.025
100. Grossman M et al (2002) Information processing speed and sentence comprehension in Parkinson's disease. Neuropsychology 16:174–181. https://doi.org/10.1037//0894-4105.16.2.174
101. Kotz SA, Schmidt-Kassow M (2015) Basal ganglia contribution to rule expectancy and temporal predictability in speech. Cortex 68:48–60. https://doi.org/10.1016/J.CORTEX.2015.02.021
102. Sapir S (2014) Multiple factors are involved in the dysarthria associated with Parkinson's disease: a review with implications for clinical practice and research. J Speech Lang Hear Res 57:1330–1343. https://doi.org/10.1044/2014_JSLHR-S-13-0039
103. Sörös P et al (2017) Increase in beta-band activity during preparation for overt speech in patients with Parkinson's disease. Front Hum Neurosci 11:371. https://doi.org/10.3389/fnhum.2017.00371
104. Mallet N et al (2008) Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex. J Neurosci 28:4795–4806. https://doi.org/10.1523/JNEUROSCI.0123-08.2008
105. Law J et al (2000) Prevalence and natural history of primary speech and language delay: findings from a systematic review of the literature. Int J Lang Commun Disord 35:165–188. https://doi.org/10.1080/136828200247133
106. Newbury DF, Fisher SE, Monaco AP (2010) Recent advances in the genetics of language impairment. Genome Med 2:6. https://doi.org/10.1186/gm127
107. Tomblin B (2011) Co-morbidity of autism and SLI: kinds, kin and complexity. Int J Lang Commun Disord 46:127–137. https://doi.org/10.1111/j.1460-6984.2011.00017.x
108. Vargha-Khadem F, Gadian DG, Copp A, Mishkin M (2005) FOXP2 and the neuroanatomy of speech and language. Nat Rev Neurosci 6:131–138. https://doi.org/10.1038/nrn1605
109. Watkins RV, Yairi E, Ambrose NG (1999) Early childhood stuttering III. J Speech Lang Hear Res 42:1125–1135. https://doi.org/10.1044/jslhr.4205.1125
110. Bishop DV (2017) Why is it so hard to reach agreement on terminology? The case of developmental language disorder (DLD). Int J Lang Commun Disord 52:671–680. https://doi.org/10.1111/1460-6984.12335
111. Tomas E, Vissers C (2019) Behind the scenes of developmental language disorder: time to call neuropsychology back on stage. Front Hum Neurosci 12:1–10. https://doi.org/10.3389/fnhum.2018.00517
112. Helen T-F, Cooper J (1999) Present and future possibilities for defining a phenotype for specific language impairment. J Speech Lang Hear Res 42:1275–1278. https://doi.org/10.1044/jslhr.4205.1275
113. Tomblin JB et al (1997) Prevalence of specific language impairment in kindergarten children. J Speech Lang Hear Res 40:1245–1260. https://doi.org/10.1044/jslhr.4006.1245
114. Evans JL, Brown TT (2016) Chapter 72 – Specific language impairment. In: Hickok G, Small SL (eds) Neurobiology of language. Academic Press, San Diego, pp 899–912
115. Pijnacker J et al (2017) Semantic processing of sentences in preschoolers with specific language impairment: evidence from the N400 effect. J Speech Lang Hear Res 60:627–639. https://doi.org/10.1044/2016_JSLHR-L-15-0299
116. Evans JL, Selinger C, Pollak SD (2011) P300 as a measure of processing capacity in auditory and visual domains in specific language impairment. Brain Res 1389:93–102. https://doi.org/10.1016/j.brainres.2011.02.010
117. Yairi E, Ambrose N (2013) Epidemiology of stuttering: 21st century advances. J Fluen Disord 38:66–87. https://doi.org/10.1016/j.jfludis.2012.11.002
118. Etchell AC et al (2018) A systematic literature review of neuroimaging research on developmental stuttering between 1995 and 2016. J Fluen Disord 55:6–45. https://doi.org/10.1016/j.jfludis.2017.03.007
119. Kaganovich N, Wray AH, Weber-Fox C (2010) Non-linguistic auditory processing and working memory update in pre-school children who stutter: an electrophysiological study. Dev Neuropsychol 35:712–736.

https://doi.org/10.1080/87565641.2010.508549

120. Piispala J et al (2017) Atypical brain activation in children who stutter in a visual Go/Nogo task: an ERP study. Clin Neurophysiol 128:194–203. https://doi.org/10.1016/j.clinph.2016.11.006
121. Kreidler K, Hampton WA, Usler E, Weber C (2017) Neural indices of semantic processing in early childhood distinguish eventual stuttering persistence and recovery. J Speech Lang Hear Res 60:3118–3134. https://doi.org/10.1044/2017_JSLHR-S-17-0081
122. Vallar G et al (1988) Recovery from aphasia and neglect after subcortical stroke: neuropsychological and cerebral perfusion study. J Neurol Neurosurg Psychiatry 51:1269–1276. https://doi.org/10.1136/jnnp.51.10.1269
123. Wallesch C-W, Blanken G (2000) Recurring utterances—how, where, and why are they generated? Brain Lang 71:255–257. https://doi.org/10.1006/brln.1999.2263
124. Wallesch C-W (2003) Sprache. In: Karnath H-O, Thier P (eds) Neuropsychologie. Springer, Berlin, Heidelberg, pp 551–555
125. Wallesch C-W (1985) Two syndromes of aphasia occurring with ischemic lesions involving the left basal ganglia. Brain Lang 25:357–361. https://doi.org/10.1016/0093-934X(85)90090-2
126. Wallesch CW, Papagno C (1988) Subcortical aphasia. In: Aphasia. Whurr Publishers, London, pp 256–287
127. Tankus A, Fried I (2019) Degradation of neuronal encoding of speech in the subthalamic nucleus in Parkinson's disease. Neurosurgery 84:378. https://doi.org/10.1093/neuros/nyy027
128. Crosson B (1985) Subcortical functions in language: a working model. Brain Lang 25:257–292. https://doi.org/10.1016/0093-934X(85)90085-9
129. Cappa SF, Vignolo LA (1979) "Transcortical" features of aphasia following left thalamic hemorrhage. Cortex 15:121–129. https://doi.org/10.1016/S0010-9452(79)80012-X
130. Crosson B et al (1999) Mapping of semantic, phonological, and orthographic verbal working memory in normal adults with functional magnetic resonance imaging. Neuropsychology 13:171. https://doi.org/10.1037/0894-4105.13.2.171
131. Raymer AM et al (1997) Lexical–semantic deficits in two patients with dominant thalamic infarction. Neuropsychologia 35:211–219. https://doi.org/10.1016/S0028-3932(96)00069-3
132. Nadeau SE, Crosson B (1997) Subcortical aphasia. Brain Lang 58:355–402. https://doi.org/10.1006/brln.1997.1707
133. Weiller C et al (1993) The case of aphasia or neglect after striatocapsular infarction. Brain 116:1509–1525. https://doi.org/10.1093/brain/116.6.1509
134. Adolphs R, Damasio H, Tranel D (2002) Neural systems for recognition of emotional prosody: a 3-D lesion study. Emotion 2:23–51. https://doi.org/10.1037/1528-3542.2.1.23
135. Baum SR, Pell MD (1999) The neural bases of prosody: insights from lesion studies and neuroimaging. Aphasiology 13:581–608. https://doi.org/10.1080/026870399401957
136. Buchanan TW et al (2000) Recognition of emotional prosody and verbal components of spoken language: an fMRI study. Cogn Brain Res 9:227–238. https://doi.org/10.1016/S0926-6410(99)00060-9
137. Wildgruber D et al (2004) Distinct frontal regions subserve evaluation of linguistic and emotional aspects of speech intonation. Cereb Cortex 14:1384–1389. https://doi.org/10.1093/cercor/bhh099
138. Lieberman P (2001) Human language and our reptilian brain: the subcortical bases of speech, syntax, and thought. Perspect Biol Med 44:32–51. https://doi.org/10.1353/pbm.2001.0011
139. Albuquerque L et al (2016) Advanced Parkinson disease patients have impairment in prosody processing. J Clin Exp Neuropsychol 38:208–216. https://doi.org/10.1080/13803395.2015.1100279
140. Breitenstein C et al (2001) Impaired perception of vocal emotions in Parkinson's disease: influence of speech time processing and executive functioning. Brain Cogn 45:277–314. https://doi.org/10.1006/BRCG.2000.1246
141. Pell MD, Leonard CL (2003) Processing emotional tone from speech in Parkinson's disease: a role for the basal ganglia. Cogn Affect Behav Neurosci 3:275–288. https://doi.org/10.3758/CABN.3.4.275
142. Pell MD, Cheang HS, Leonard CL (2006) The impact of Parkinson's disease on vocal-prosodic communication from the perspective of listeners. Brain Lang 97:123–134. https://doi.org/10.1016/j.bandl.2005.08.010

143. Pell MD, Leonard CL (2005) Facial expression decoding in early Parkinson's disease. Cogn Brain Res 23:327–340. https://doi.org/10.1016/j.cogbrainres.2004.11.004
144. Catani M, Mesulam M (2008) The arcuate fasciculus and the disconnection theme in language and aphasia: history and current state. Cortex 44:953–961. https://doi.org/10.1016/j.cortex.2008.04.002
145. Friederici AD (2012) The cortical language circuit: from auditory perception to sentence comprehension. Trends Cogn Sci 16:262–268. https://doi.org/10.1016/j.tics.2012.04.001
146. Hagoort P (2019) The neurobiology of language beyond single-word processing. Science 366:55–58. https://doi.org/10.1126/science.aax0289
147. Hickok G, Poeppel D (2007) The cortical organization of speech processing. Nat Rev Neurosci 8:393–402. https://doi.org/10.1038/nrn2113
148. Hartwigsen G (2016) Adaptive plasticity in the healthy language network: implications for language recovery after stroke. Neural Plast 2016:e9674790. https://doi.org/10.1155/2016/9674790
149. Hage SR, Nieder A (2016) Dual neural network model for the evolution of speech and language. Trends Neurosci 39:813–829. https://doi.org/10.1016/j.tins.2016.10.006
150. Price CJ (2010) The anatomy of language: a review of 100 fMRI studies published in 2009. Ann N Y Acad Sci 1191:62–88. https://doi.org/10.1111/j.1749-6632.2010.05444.x
151. Perani D et al (2011) Neural language networks at birth. Proc Natl Acad Sci 108:16056–16061. https://doi.org/10.1073/pnas.1102991108
152. Barbas H, García-Cabezas MÁ, Zikopoulos B (2013) Frontal-thalamic circuits associated with language. Brain Lang 126:49–61. https://doi.org/10.1016/j.bandl.2012.10.001
153. Utianski RL et al (2019) Electroencephalography in primary progressive aphasia and apraxia of speech. Aphasiology 33:1410–1417. https://doi.org/10.1080/02687038.2018.1545991
154. Marangolo P (2020) The potential effects of transcranial direct current stimulation (tDCS) on language functioning: combining neuromodulation and behavioral intervention in aphasia. Neurosci Lett 719:133329. https://doi.org/10.1016/j.neulet.2017.12.057
155. Wortman-Jutt S, Edwards DJ (2017) Transcranial direct current stimulation in post-stroke aphasia recovery. Stroke 48:820–826. https://doi.org/10.1161/STROKEAHA.116.015626
156. Torres J, Drebing D, Hamilton R (2013) TMS and tDCS in post-stroke aphasia: integrating novel treatment approaches with mechanisms of plasticity. Restor Neurol Neurosci 31:501–515. https://doi.org/10.3233/RNN-130314
157. Thiel A et al (2013) Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. Stroke 44:2240–2246. https://doi.org/10.1161/STROKEAHA.111.000574
158. Norise C, Hamilton RH (2017) Non-invasive brain stimulation in the treatment of post-stroke and neurodegenerative aphasia: parallels, differences, and lessons learned. Front Hum Neurosci 10:675. https://doi.org/10.3389/fnhum.2016.00675
159. Rektorová I, Anderková Ľ (2017) Chapter thirty-eight – noninvasive brain stimulation and implications for nonmotor symptoms in Parkinson's disease. In: Chaudhuri KR, Titova N (eds) International review of neurobiology. Academic Press, pp 1091–1110
160. Lee HK et al (2019) Does transcranial direct current stimulation improve functional locomotion in people with Parkinson's disease? A systematic review and meta-analysis. J Neuroeng Rehabil 16:84. https://doi.org/10.1186/s12984-019-0562-4
161. Zanjani A, Zakzanis KK, Daskalakis ZJ, Chen R (2015) Repetitive transcranial magnetic stimulation of the primary motor cortex in the treatment of motor signs in Parkinson's disease: a quantitative review of the literature. Mov Disord 30:750–758. https://doi.org/10.1002/mds.26206
162. Teichmann M et al (2016) Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia. Ann Neurol 80:693–707. https://doi.org/10.1002/ana.24766
163. McConathey EM et al (2017) Baseline performance predicts tDCS-mediated improvements in language symptoms in primary progressive aphasia. Front Hum Neurosci 11:347. https://doi.org/10.3389/fnhum.2017.00347
164. Ficek BN et al (2018) The effect of tDCS on functional connectivity in primary progressive aphasia. Neuroimage Clin 19:703–715. https://doi.org/10.1016/j.nicl.2018.05.023

165. Ladányi E et al (2020) Is atypical rhythm a risk factor for developmental speech and language disorders? Wiley Interdiscip Rev Cogn Sci 11:e1528. https://doi.org/10.1002/wcs.1528
166. Alajouanine TH, Lhermitte F (1965) Acquired aphasia in children. Brain 88:653–662. https://doi.org/10.1093/brain/88.4.653
167. Vicari S et al (2000) Plasticity and reorganization during language development in children with early brain injury. Cortex 36:31–46. https://doi.org/10.1016/S0010-9452(08)70834-7
168. Dronkers NF, Ivanova MV, Baldo JV (2017) What do language disorders reveal about brain-language relationships? From classic models to network approaches. J Int Neuropsychol Soc 23:741–754. https://doi.org/10.1017/S1355617717001126