Brain Struct Funct (2010) 214:419–433
DOI 10.1007/s00429-010-0257-x

REVIEW

The contribution(s) of the insula to speech production: a review of the clinical and functional imaging literature

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Received: 7 December 2009 / Accepted: 21 April 2010 / Published online: 29 May 2010

Abstract Skilled spoken language production requires fast and accurate coordination of up to 100 muscles. A long-standing concept—tracing ultimately back to Paul Broca—assumes posterior parts of the inferior frontal gyrus to support the orchestration of the respective movement sequences prior to innervation of the vocal tract. At variance with this tradition, the insula has more recently been declared the relevant "region for coordinating speech articulation", based upon clinico-neuroradiological correlation studies. However, these findings have been criticized on methodological grounds. A survey of the clinical literature (cerebrovascular disorders, brain tumours, stimulation mapping) yields a still inconclusive picture. By contrast, functional imaging studies report more consistently hemodynamic insular responses in association with motor aspects of spoken language. Most noteworthy, a relatively small area at the junction of insular and opercular cortex was found sensitive to the phonetic-linguistic structure of verbal utterances, a strong argument for its engagement in articulatory control processes. Nevertheless, intrasylvian hemodynamic activation does not appear restricted to articulatory processes and might also be engaged in the adjustment of the autonomic system to ventilatory needs during speech production: Whereas the posterior insula could be involved in the cortical representation of respiration-related metabolic (interoceptive) states, the more rostral components, acting upon autonomic functions, might serve as a corollary pathway to "voluntary control of breathing" bound to corticospinal and -bulbar fiber tracts. For example, the insula could participate in the implementation of task-specific autonomic settings such as the maintenance of a state of relative hyperventilation during speech production.

Keywords Insula · Speech motor control · Articulation · Speech breathing · Respiration

Introduction

Postmortem examination of the brain of a patient, almost mute for many years prior to his death—verbal output was restricted to the syllble "tan"—led Broca (1861) to his famous conclusion that the foot of the third frontal gyrus engages in speech production, more specifically, the "faculty to coordinate the movements subserving spoken language" ("faculté de coordonner les mouvements propres au language", p. 333; for a review see Caplan 1987). A subsequent publication assigned, more specifically, the relevant area to the inferior frontal convolution of the left hemisphere (Broca 1865). In 1874, Carl Wernicke, a then 26-year-old physician, postulated on the grounds of clinical and neuropathological data that speech comprehension predominantly depends upon posterior parts of the ipsilateral superior temporal gyrus. Whereas the notion of an anterior and posterior perisylvian "language zone", bound at least in right-handers to the left hemisphere, has become a

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classical topos of clinical neurology, it is less well-known that already back in 1874 Wernicke predicted a third distinct syndrome of acquired speech/language deficits, i.e., conduction aphasia, linked to damage to the island of Reil, a cortical area which in his opinion interconnected rostral and caudal perisylvian regions. He abandoned, however, this concept several years later, assuming the disruption of adjacent fiber tracts to represent the decisive pathomechanism (Henderson 1992; for a review of the early literature see, e.g., Goldstein 1948). A revival of Wernicke's original model of conduction aphasia in the work of Goldstein (1911)—this author introduced the term "central aphasia"—did not have a lasting impact upon the field.

More recently, the island of Reil (synonyms: insula, insular cortex, floor of intrasylvian cortex, floor of Sylvian fissure) was brought again into the focus of speech/language pathology: Clinico-neuroradiological correlation studies proposed apraxia of speech (AOS)—a syndrome assumed to reflect impaired higher-order aspects of speech motor control, i.e., the "planning" of the respective vocal tract movement sequences—to be associated with lesions of the language-dominant anterior insula, more specifically, the superior part of the intrasylvian precentral gyrus (Dronkers 1996). However, these data have been criticized, among others, on methodological grounds (Hillis et al. 2004; see below). Considering, furthermore, the well-established participation of the anterior insula in phylogenetically rather old perceptual-motor functions such as feeding-related behaviour (Rizzolatti and Sinigaglia 2006) or the maintenance of homeostatic balance (Craig 2002, 2003), it is a bit bewildering that "motor planning of speech" (Dronkers 1996) or "motor articulatory planning" (Nestor et al. 2003), capacities unique to our species, might depend upon the rostral, i.e., "paralimbic" component of intrasylvian cortex. Nevertheless, functional imaging consistently reported hemodynamic activation of intrasylvian cortex in association with motor aspects of speech production. As its aim, this review tries to test the highly controversial suggestion of a tight association between AOS and insular pathology, based upon lesion-overlap studies, against (1) the available case histories of damage more or less restricted to the floor of the Sylvian fissure, including pre- and intraoperative electrical stimulation of insular structures, and (2) the available functional imaging investigations addressing motor aspects of spoken language. At first, the frontal network participating in speech motor control (Fig. 1) as well as the clinical features of AOS will be briefly delineated. These data provide a basis for the understanding of the speech/language deficits subsequent to intrasylvian pathology and the hemodynamic activation patterns bound to speech production.

Compartmentalization of speech motor control at the level of the frontal lobe

Primary motor representation of the vocal tract and corticobulbar tracts

Speech production poses considerable demands on motor control mechanisms, requiring fast and accurate (skilled) execution of orofacial gestures properly adjusted in time and range to laryngeal as well as respiratory activities (e.g., Kent 1997). Altogether, up to 100 muscles have to be coordinated during verbal communication. Skilled motor tasks depend upon the integrity of primary motor cortex and its efferent fiber tracts (Brooks 1986). Apart from a few exceptions, e.g., the lower facial musculature, the brainstem nuclei projecting to the vocal tract receive input from both cerebral hemispheres each. Electrical stimulation of the exposed motor strip of either hemisphere in awake subjects during brain surgery (intraoperative stimulation mapping), thus, may elicit sustained or interrupted "vowel cries" (Penfield and Roberts 1959). Therefore, unilateral dysfunctions of the primary motor representation of vocal tract structures and/or corticobulbar tracts yield, if at all, a transient reduction of the strength of vocal tract muscles and, as a rule, fail to elicit significant and/or persistent speech motor deficits (Ackermann and Ziegler 2010). By contrast, bilateral damage to the respective upper motor neurons gives rise to the syndrome of "spastic dysarthria" characterized, among others, by slowed speech tempo, reduced range of orofacial movements, and hyperadduction of the vocal folds (Murdoch et al. 1997). At its extreme, this constellation may result into anarthria and/or aphonia, i.e., a complete inability to voluntarily "steer" vocal tract muscles (Foix-Chavany-Marie syndrome, bilateral opercular syndrome, or pseudobulbar palsy; for a review see Ackermann et al. 2010).

Most noteworthy, patients with Foix-Chavany-Marie syndrome or pseudobulbar palsy may show preserved voiced phonation and orofacial movements during affective vocalizations such as laughter and crying, in the presence of severely impaired or even abolished active control of the muscles supplied by the lower cranial nerves ("dramatic automatic-voluntary movement dissociation"; Mao et al. 1989). In these subjects, furthermore, compromised innervation of the vocal tract subsequent to bilateral disruption of the respective upper motor neurons may cause a release or disinhibition of nonverbal affective vocalizations (pathological laughter/crying). Conceivably, these emotional "bursts" are mediated by a "limbic vocalization system", projecting, as delineated in subhuman primates, from the anterior cingulate cortex (ACC) via periaqueductal gray (PAG) and a pontine vocal pattern generator to cranial nerve nuclei of the brainstem (Jürgens

2002; Hage and Jürgens 2006). Most presumably, primate vocal pattern generators trace back to neural circuits already present in early fishes, located within a caudal hindbrain/rostral spinal compartment (Bass et al. 2008). Thus, two distinct cerebral pathways appear to act upon the motor nuclei of the lower cranial nerves in humans ("dual pathway" model of acoustic communication; see Ackermann and Ziegler 2010).

Medial wall of the frontal lobes: supplementary motor area and anterior cingulate cortex

Patients suffering from damage to supplementary motor area (SMA) of the language-dominant hemisphere may exhibit reduced spontaneous verbal behavior, in the absence of any central-motor disorders of the vocal tract muscles and any deterioration of language functions. This pattern of disrupted acoustic communication has been considered a variant of transcortical motor aphasia (Freedman et al. 1984). A similar profile of speech/language pathology may emerge after disruption of the fiber tracts linking SMA to the rostral perisylvian cortex which curve around the anterior horn of the lateral ventricle. Furthermore, bilateral damage to mesiofrontal areas, presumably, encroaching upon anterior cingulate cortex (ACC) and its projections to SMA, may give rise to the syndrome of akinetic mutism, characterized by a lack of self-initiated motor activities, including speech production (Ackermann et al. 2010). In consideration of these clinical data, the medial walls of the frontal lobes appear to support motivational aspects of verbal motor behavior, and SMA has been assumed, more specifically, to operate as a "starting mechanism of speech" (Botez and Barbeau 1971). Apart from reduced spontaneous speech production, the verbal utterances of patients suffering from mesiofrontal lesions may be characterized by 'flat' and monotonous intonation (Rubens 1975; Jürgens and von Cramon 1982), resembling the syndrome of motor aprosodia subsequent to dysfunctions of the basal ganglia (Cancelliere and Kertesz 1990). In addition, dysfluent, i.e., stuttering-like speech utterances in terms of sound prolongations and syllable repetitions have also been observed in subjects with damage to the medial wall of the language-dominant frontal lobe (see, e.g., Ziegler et al. 1997).

Lower (opercular) precentral convolution and posterior parts of inferior frontal gyrus (Broca's area)

Besides spastic dysarthria (primary motor representation of vocal tract muscles/corticobulbar tracts) and transcortical motor aphasia (left-hemisphere mesiofrontal cortex and its projections to fronto-opercular regions), AOS is considered a further distinct set of speech production deficits, arising from lesions of the language-dominant frontal lobe. This syndrome is characterized by (1) effortful and groping speech gestures concomitant with self-corrections, (2) dysprosody, i.e., abnormal intonation, rhythm, and accentuation of spoken language, (3) inconsistent articulatory errors (awkward and ill-formed speech sounds) across productions of the same item ("phonetic variability"), and (4) impaired initiation of speech utterances (Ziegler 2008; Ogar et al. 2005). As a consequence, a hesitant-halting and dysfluent mode of verbal communication emerges, including false starts, repairs, and repetitive attempts at speech initiation. Articulatory errors show characteristic frequency effects across test materials (consonant clusters more affected (>) than single consonants, nonsense words >lexical entries); nevertheless, even in severe constellations entire words or phrases may sometimes be produced accurately ("islands of preserved speech"). Prolonged pauses between syllables and words are often observed, giving rise to a reduced overall speaking rate. The clinical history of AOS varies across subjects, ranging from brief episodes of speech deficits to persistent severe abnormalities. By contrast to spastic dysarthria, subjects do not exhibit weakness or slowness of vocal tract gestures during speech production. In other words, movement execution in terms of muscle strength and range is unimpaired. Therefore, this syndrome of articulatory/phonatory deficits is considered a higher-level dysfunction of speech motor control, reflecting, e.g., "inefficiencies in the translation of a well-formed and filled phonological frame to previously learned kinematic parameters" (McNeil et al. 1997).

Tracing back ultimately to the work of Broca (1861), AOS used to be attributed to pathology of either the opercular part of the inferior frontal convolution and/or the ventral parts of the lateral aspect of the precentral gyrus (ventrolateral precentral convolution) and/or the white matter deep to both structures within the language-dominant hemisphere (Schiff et al. 1983; Alexander et al. 1989; for a recent review see Ziegler 2008). For example, damage restricted to the so-called Broca area, i.e., posterior parts of the inferior frontal gyrus, gives rise to initial mutism, rapidly evolving into verbal apraxia of a more or less transient nature, rather than the "more complex syndrome traditionally referred to as Broca aphasia". Most often, however, verbal apraxia emerges within the context of non-fluent aphasia syndromes and not as an isolated constellation (Ziegler 2008). In line with the notion that damage to ventrolateral aspects of the frontal lobe represents the decisive lesion site in verbal apraxia, electrical stimulation of left-hemisphere opercular structures rostral to primary motor cortex has been found to elicit speech arrest as well as an inability to mimic single articulatory gestures (Ojemann 1994). The latter area, therefore, was assumed to operate as a "final motor pathway for speech".

A controversial further component of the cerebral network of speech motor control: the anterior insula ("paralimbic" component of intrasylvian cortex)

Patient "Tantan" (Broca 1861) showed a large infarction of the left hemisphere which extended far beyond the so-called Broca area, encroaching, among others, upon insular cortex. More recent clinical studies also found the "more complex syndrome traditionally referred to as Broca aphasia" to depend upon rather widespread lesions, often encompassing intrasylvian areas (Mohr et al. 1978; Mazzocchi and Vignolo 1979). These observations raise the question of whether and in how far the insula participates specifically in speech/language processing. Based upon the reconstruction of focal brain lesions from computerized tomography (CT) and magnetic resonance imaging (MRI) scans in 25 stroke patients with AOS, Dronkers (1996) found "a discrete region of the left precentral gyrus of the insula" to represent the area of maximum overlap of cerebrovascular pathology. Most noteworthy, this component was completely spared in 19 subjects lacking verbal apraxia, indicating a robust double dissociation between AOS and insular lesion site (see also Ogar et al. 2006). However, these findings have been criticized on methodological grounds (Hillis et al. 2004). More specifically, the lesion-overlap investigations cannot rule out "that all patients with apraxia of speech have insular damage, but that few patients with insular damage have apraxia of speech" (p. 1480). In consideration of these caveats, patients with damage restricted to the insula of Reil should provide a feasible control condition for the evaluation of the proposed relationship with AOS.

Speech/language functions and insular cortex: clinical studies

Cerebrovascular disorders (ischemic infarctions)

Ischemic damage restricted, by and large, to intrasylvian cortex represents a highly rare event. For example, Goldstein (1948, p. 240) was aware of just a single representative case among the relevant literature of the late nineteenth and the early twentieth century. Recent surveys of large groups of patients suffering from an infarction within the area of blood supply of the medial cerebral artery (MCA) also report a very low incidence of "isolated" insular pathology. Thus, only four individuals could be identified among the 4,800 consecutive cases of a first-ever cerebrovascular disorder entered between 1990 and 1999 into the Lausanne Stroke Registry (Cereda et al. 2002). MRI brain scans revealed, however, damage to the posterior (!) sector of intrasylvian cortex in all four subjects. Nevertheless, the two instances of left-sided pathology had given rise to articulatory deficits ("dysarthria") concomitant with a syndrome of fluent (case 2) or nonfluent (case 3) aphasia, though sparing the anterior insula. As a further example, another relatively large cohort of patients ($n = 208$), based upon comparable inclusion criteria, did not encompass a single instance of a lesion restricted to the insular cortex (Colivicchi et al. 2005). By contrast, intrasylvian pathology is often embedded into larger territorial ischemic infarctions within the area of MCA blood supply. For example, a major or minor insular lesion could be detected in about half the cases out of a total of 150 consecutive patients with nonlacunar MCA stroke (Fink et al. 2005).

A variety of clinical studies tried to determine the influence of insular damage upon the autonomic system, especially, its impact upon cardiovascular (e.g., Sander et al. 2001) or metabolic parameters (Allport et al. 2004). Unfortunately, data on speech/language pathology are, as a rule, not provided. One of those studies reported, however, mutism after "complete left insula infarction associated with minor involvement of some adjacent structures, such as the temporal operculum and putamen" (Fink et al. 2005). The patient, furthermore, presented with "right facial weakness", in the absence of other focal neurological signs, indicating damage to the efferent projections of the "mouth area" of left-hemisphere primary motor cortex. A lesion extending from intrasylvian areas to the corticobulbar tracts must be expected to encroach also upon the white matter underneath the opercular parts of the precentral and the inferior frontal gyrus. In line with this suggestion, visual inspection of the MRI scans points at an "undercutting" of the adjacent fronto-opercular structures (see Fig. 1 in Fink et al. 2005). Most noteworthy, this study also noticed that "isolated anterior insula infarcts were often accompanied by other infarcts in the superior MCA division territory" (p. 1084).

Given the rarity of "isolated" insular lesions, it is not surprising that only a few case reports specifically addressing the communication disorders in such constellations are available so far. Most noteworthy, the observed profiles of speech/language deficits mostly do not fit into the concept of AOS. Thus, Alexander et al. (1987) were able to identify two patients with damage to the insula—its medial [sic] part and the subjacent white matter (extreme/external capsule)—among a larger series of subjects with subcortical cerebrovascular disorders. In both instances, a mild fluent aphasia, characterized by word-finding difficulties, rare phonemic paraphasias during conversation, impaired repetition (in one of the two patients), and agraphia, could be noted, in the absence both of non-/dysfluent speech utterances as well as articulatory abnormalities ("dysarthria"). A subsequent case study noted, among

others, "difficulty in initiating speech and pronouncing words… aberrant linguistic prosody with occasional phonemic and rare semantic paraphasias… and poor repetition" subsequent to an infarction of the left anterior insula "with pressure on hte extreme capsule and claustrum" (Shuren 1993). In addition, however, the neuroradiological investigations revealed lacunar infarcts within the putamen at either side. Nevertheless, this patient showed almost normal spoken language during a state of emotional arousal, a phenomenon strongly arguing against verbal apraxia. A typical AOS syndrome could be documented in a patient with damage to the sulcus circularis and the gyri breves of the left insula, extending, however, to the pars opercularis of the inferior frontal gyrus (Marien et al. 2001). So, again, the speech deficits cannot be assigned with certainty to a dysfunction restricted to the floor of the Sylvian fissure. To the best of our knowledge, only a single clinical study focuses on the communication disorders in a patient with a lesion, by and large, restricted to the precentral gyrus of the insula (Nagao et al. 1999). This subject experienced sudden onset of "aphonia"—most presumagly, the authors refer to a state of mutism—and oro-lingual apraxia, in the absence of any other neurological signs. Most noteworthy, he "could speak" again after 12 h and fully recovered within 24 h. In the light of these follow-up data, the initial state of mutism again cannot unambiguously be attributed to the insular lesion. As a plausible alternative, transient hypoperfusion and subsequent inactivation of adjacent peri-lesional speech-relevant structures ("ischemic penumbra") might have given rise to the observed rapidly resolving deficits of spoken language. Since the case study referred to did not document the area of potentially reversible ischemic dysfunctions, by comparison of diffusion- and perfusion-weighted images, this issue must remain an open question.

In the available literature, speech/language deficits were almost exclusively associated with damage to the left-hemisphere insula. As an exception to this rule, "a bilateral opercular syndrome" could be observed in a right-handed patient with an ischemic infarction "involving the whole right insula and the inner cortical surface on the right frontotemporalparietal operculum" at autopsy, in the absence of any lesions within the contralateral hemisphere (Starkstein et al. 1988). This subject suffered from severe or even complete bilateral weakness of the orofacial muscles, rendering him completely speechless. Comprehension both of spoken language and texts was, by and large, found preserved, and the subject was able to communicate within the written modality. Besides bilateral paresis of vocal tract structures, pointing at a dysfunction of the upper motor neurons, the authors assume the presence of aphemia—in the literature, usually, a synonym for apraxia of speech. The clinical data do not allow, however, for an unambiguous diagnosis of this syndrome. Anyway, this patient presents with a so far singular, and difficult to explain, clinicopathologic constellation.

Tracing back to the "classical connectionist models" of Wernicke (1874) and Lichtheim (1885; for a review see Caplan 1987), conduction aphasia is recognized as a distinct variant of acquired speech/language disorders subsequent to brain damage, characterized by "fluent, meaningful speech … profound verbal repetition defect (with either entire blocking of repetition or repetition with phonemic paraphasias) … and preserved or minimally impaired aural comprehension defect" (Damasio and Damasio 1980). In parentheses, more recent research, based upon psycholinguistic computational models, points at different subtypes of conduction aphasia (see, e.g., Sidiropoulos et al. 2008). Rather than damage to intrasylvian cortex proper, a widely acknowledged concept suggests disruption of the arcuate fasciculus—a fiber tract connecting temporo-parietal structures with lower frontal region—to represent a salient pathomechanism of this syndrome ("disconnection syndrome"; Geschwind 1965). Besides damage to caudal parts of those fiber tracts underneath the supramarginal gyrus (Benson et al. 1973), destruction of white matter at the level of the extreme capsule adjacent to the insula has been considered a "decisive pathological element" of conduction aphasia (Damasio and Damasio 1980). A more recent investigation, based upon a series of 107 consecutive patients with first-ever stroke, documented by means of magnetic resonance imaging (MRI), again found "repetition disorders" to be associated with "insula-external capsule lesions" (Kreisler et al. 2000).

Pre- and postoperative sequels of brain tumors

Besides cerebrovascular disorders, brain tumors represent a further clinical paradigm for the evaluation of the impact of intrasylvian lesions upon speech/languge functions. Patients suffering from a tumor restricted to or encroaching upon the floor of the left Sylvian fissure may lack any speech/language deficits prior to surgery (Ebeling and Kothbauer 1995), and even after subsequent complete removal of insular and opercular cortex (Kumabe et al. 1998). A large series of patients ($n = 177$) with tumors of the "limbic and paralimbic systems" included 57 cases with "insula tumours", most of them extended, however, to fronto- and temporo-opercular cortex (Yasargil et al. 1992). About a quarter of the latter subgroup of individuals (15/57) showed "speech impairment" at clinical examination, "usually manifest as word-finding difficulty". Another relatively large cohort of 30 consecutive patients suffering from an intrinsic tumor involving the insula provides more specific data. In five subjects, pathology was

found restricted to the floor of the lateral sulcus, in three cases affecting the left hemisphere (Zentner et al. 1996). None of these individuals showed any focal neurological signs, including aphasia and/or apraxia, 3 or 9 months after microsurgical treatment (complete or nearly complete resection). And a more recent study reported uncompromised speech motor control after removal of the entire insula of the language-dominant hemisphere in a patient with frontal glioma, and the "mild language disturbances" prior to surgery ("slowness of speech, phonemic paraphasia and anomia") even receded after resection (Duffau et al. 2001). Conceivably, slowly evolving pathological processes such as brain tumors allow for a reorganization of speech/language functions. Assuming contralateral insular compensation as one potential mechanism, persisting AOS must be expected subsequent to damage to intrasylvian cortex at both sides. A single case of bilateral insular lesions–two ischemic infarctions at an interval of a few days—has been reported so far (Habib et al. 1995). Within both hemispheres, the lesion was centered around the insular cortex, extending, however, far into the adjacent white matter up to the head of the caudate nucleus at the left, and encroaching upon the frontoparietal opercular cortex as well as the superior temporal gyrus at the right side. Given a tight association between anterior insula and higher-order aspects of speech motor control, distinct articulatory/phonatory deficits must be expected under these conditions, even if inter-hemispheric reorganization may take place in AOS patients. However, the patient showed "no attempt at communicating (whether verbal, written or by gesture)", and the authors note that the observed "communicative indifference" resembles the behavior of subjects with damage to left-hemisphere anterior cingulate cortex and supplementary motor area. More specifically, this constellation reminds of akinetic mutism associated with bilateral lesions of rostral mesiofrontal cortex (see Ackermann and Ziegler 2010). In line with this suggestion, the observed sequels of bilateral insular pathology are also similar to transient cerebellar mutism which, as demonstrated by functional imaging studies, appears to reflect distance effects ("diaschisis") in terms of bilateral mesiofrontal hypometabolism (see Ackermann et al. 2007). By contrast, AOS patients with initial speechlessness, as a rule, show effortful attempts at shaping speech sounds and/or use efficiently other modes of communication such as written language (Ziegler 2008). It cannot be excluded, however, that this constellation of "communicative indifference" might have masked additional articulatory disorders. Nevertheless, there is preliminary evidence that insular structures, indeed, might engage in compensation of speech/language functions. A recent fMRI study investigated the topographic pattern of hemodynamic activation during verbal fluency tasks in subjects with left-hemisphere temporal lobe epilepsy and in healthy controls (Voets et al. 2006). Most noteworthy, the patients displayed a shift of frontal response peaks towards the insula at the right side. The adaptive role of these distributional changes of hemodynamic activation subsequent to dysfunctions of the language-dominant perisylvian cortex remains to be established.

Brain tumors may give rise to epileptic fits affecting an individual's vocal/verbal behaviour (e.g., Ackermann et al. 1996). Thus, a patient suffering from an insular glioma produced regularly the phrase "stop—be quiet" during seizures, concomitant with abnormal sensations in her stomach and throat (Yasargil et al. 1992). Pathology extended, however, into mesiobasal and lateral temporal structures, and the "vocalizations", therefore, cannot be unambiguously assigned to a focus within intrasylvian cortex.

Pre-/intraoperative electrical cortical stimulation

Direct electrical stimulation of the cortical surface prior to or during brain surgery provides a further approach to the investigation of the role of the insula in speech production. A seminal study by Penfield and Faulk (1955) did not, however, report any speech disturbances during intraoperative cortical mapping. However, a later study found electrical stimulation within the mid-third of intrasylvian cortex to elicit consistently naming errors—the ability to speak being preserved—in a left-hemisphere language-dominant epileptic subject (Ojemann and Whitaker 1978). As a consequence, this area was assumed to pertain to the (nonmotor) "language cortex" of the left hemisphere. By contrast, the "speech articulatory program" appeared to be confined to "a narrow band of posterior inferior frontal lobe, immediately anterior to motor strip" (for a more recent elaboration of this concept see Ojemann 1994). However, subsequent investigations were able to elicit speech arrest, more or less consistently, by means of electrical stimulation of the insula in patients suffering from drug-resistant epilepsy (Ostrowsky et al. 2000: 2/72 stimulations speech arrest, 1/72 "blurred speech", no specific topographic information) or low-grade glioma (Duffau et al. 2000: 2 subjects, responses during each stimulation of language-dominant insula).

Summary

Taken together, the available reports of ischemic infarctions more or less restricted to the insula of Reil document rather discrepant profiles of speech/language deficits in association with left, right, or bilateral pathology, most presumably, due to a varying impact upon closely adjacent white and gray matter structures also engaged in verbal

communication, i.e., fronto-opercular cortex and its connections to mesiofrontal areas and the tempororpatietal junction. This résumé is in line with the literature from the late nineteenth and early twentieth century on lesions of intrasylvian cortex (Goldstein 1948: "very different aphasic pictures are described", p. 240; see Ardila et al. 1997). As compared to the "classical" lesion sites of AOS at the lateral surface of left-hemisphere frontal lobe (e.g., Hécaen and Consoli 1973: space-occupying pathology; Alexander et al. 1989; Hillis et al. 2004: cerebrovascular disorders), the present survey of clinical data revealed less frequent and less reliable speech/language deficits in case of damage to intrasylvian cortex, and the effects of electrical cortical stimulation are also less consistent. Finally, the clinical data provided often do not allow for a differentiation between verbal apraxia and conduction aphasia (see, e.g., Griffiths et al. 2004).

Participation of the anterior insula in the control of non-speech motor functions

The suggestion that the left anterior insula supports the coordination of vocal tract muscles during speech production raises the question of a more generalized participation of intrasylvian cortex in voluntary motor control. Based upon both animal experimentation and clinical data, indeed, the insula has been assumed to represent a supplementary motor region (Augustine 1985) or a motor association area, respectively (Augustine 1996). However, only sparse clinical data in support of this concept are available so far (see Ackermann and Riecker 2004). Some studies reported that seizures due to lesions of the temporoparietal junction at either side, encroaching upon intrasylvian cortex, sometimes encompass circling or rotational movements (e.g., Schneider et al. 1971). Most presumably, however, these phenomena reflect irritation of the insular target area of projections of the thalamic vestibular relay nuclei (see, e.g., Eickhoff et al. 2006). Indeed, a neurosurgical follow-up study noted several cases of hemiparesis (4/22 patients) subsequent to the resection of tumors located within the insular region (Lang et al. 2001), but perioperative complications accounted for the observed upper limb motor deficits in all instances. Also, lower facial and/or upper limb weakness in association with insular ischemia have been attributed to a dysfunction of adjacent corticobulbar tracts (Daniels and Foundas 1997). Finally, a recent case study reported transient hemiballism, with complete recovery within 4 days, subsequent to an infarction of the posterior insula at the right (!) side (Etgen et al. 2003). However, the patient had suffered from initial hemiparesis, indicating a dysfunction extending principally beyond intrasylvian cortex and encroaching, conceivably, upon fiber tracts projecting from other cerebral structures to the basal ganglia. So, the available clinical evidence for an insular contribution to upper and lower limb, neck, or eye movements is restricted to sporadic observations which do not provide any firm support for the notion of an intrasylvian motor association area. As a further line of evidence corroborating, allegedly, the suggestion of an insular motor association area, Augustine (1996) refers to functional imaging studies addressing post-stroke motor recovery. Among others, these investigations revealed larger hemodynamic activation of the intrasylvian cortex concomitant with movements of the formerly paretic limb. In addition, the anterior insula has been assumed to pertain to a network of cerebral structures recruited during reorganization of speech and language functions subsequent to slowly evolving left-hemisphere pathology such as brain tumors (Thiel et al. 2001). Considering, however, the tight connections of the insula with the sympathetic autonomic system (see below), these findings just might reflect higher effort or attentional demands in association with recovered motor functions.

Besides AOS, nevertheless, at least two further clinical syndromes bound to the same or to overlapping muscle groups have been associated with insular lesions. First, several clinical and functional imaging data point at a contribution of intrasylvian cortex to swallowing. For example, an investigation of patients with unilateral damage to the insular cortex was able to document dysphagia in all three cases with infarction of the anterior insula, whereas a subject who had suffered ischemia of posterior intrasylvian cortex did not exhibit any swallowing problems (Daniels and Foundas 1997; for further evidence see Riecker et al. 2009). And, second, several case studies noted the presence of bucco-facial apraxia in patients suffering from, by and large, circumscribed uni- or bilateral insular lesions (Habib et al. 1995; Nagao et al. 1999). There seems to be, however, no strict co-occurrence of AOS, dysphagia, and bucco-facial apraxia in subjects with intrasylvian pathology.

In summary, the available clinical data indicate that the motor functions of the insula are, if at all, restricted to the control of vocal tract or upper midline structures, including the mimic muslces, and the most extensive evidence points at an intrasylvian contribution to swallowing, in accord with the concept of a tight association between this stretch of cortex and feeding-related activities (Rizzolatti and Sinigaglia 2006). Furthermore, the only non-speech motor responses observed during preoperative electrical stimulation of the insula in epileptic patients consisted in chewing and lipsmacking (Ostrowsky et al. 2000). Since, however, there seems to be no strict coincidence of these various motor functions, functional compartmentalization at the level of the anterior insula to some extent must be assumed.

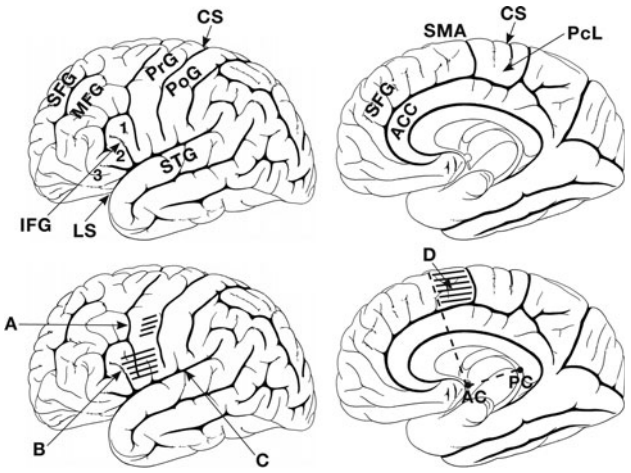

Fig. 1 *Upper row*, *left*. Several major gyri and sulci of the lateral aspect of the left hemisphere: *IFG* inferior frontal gyrus, segregating into an opercular *1*, triangular *2*, and an orbital part *3*; *MFG* middle frontal gyrus; *SFG* superior frontal gyrus; *PrG* precentral gyrus; *PoG* postcentral gyrus; *STG* superior temporal gyrus; *LS* lateral sulcus (Sylvian fissure); *CS* central sulcus (Rolandic sulcus). *Upper row, right*. Medial wall of the left hemisphere: the posterior part of SFG houses the so-called supplementary motor area (SMA 6), i.e., the medial extension of Brodmann area (BA) 6, the *dashed line* perpendicular to a plane through anterior (AC) and posterior commissure (PC) roughly corresponds to the anterior limit of SMA 6 (=SMA proper); *PcL* paracentral lobule, i.e., the medial extension of PrG and PoG; *ACC* anterior cingulate cortex. *Lower row*. The *shaded areas* (horizontal lines) refer to the cortical regions engaged in speech motor control: bilateral primar motor cortex *A*, opercular part of left IFG and lower left PrG *B*, left SMA proper *D*. In addition, the rostral part of intrasylvian cortex (anterior insula) in the depth of the lateral sulcus (LS) is assumed to contribute to speech motor control *C*. The location of the first two regions (*A*, *B*) has been derived from the respective areas of maximum hemodynamic activation as reported by a recent meta-analysis (Fox et al. 2001)

Speech/language functions and insular cortex: functional imaging data

"Minimal brain network" of speech motor control and intrasylvian cortex

Given the inconclusive and sparse clinical data, functional imaging studies might provide more decisive insights into the contribution of intrasylvian cortex to speech production. A seminal positron emission tomography (PET) investigation by Petersen et al. (1988, 1989) yielded as a "by-product" the first systematic account of hemodynamic activation patterns associated with speech motor control. The relevant brain areas included primary sensorimotor and mesiofrontal cortex (SMA) as well as anterior–superior portions of the cerebellum at either side. Quite unexpectedly, a spot "buried" in the depth of the lateral sulcus emerged, whereas both Broca's area and basal ganglia did not show any significant hemodynamic responses. In line with several preceding observations (references in Ackermann et al. 2004), a more recent PET study was able to attribute this intrasylvian hemodynamic response to the anterior insular cortex (Wise et al. 1999: significant effect only at the left side). Notwithstanding some discrepancies, the available PET and functional magnetic resonance imaging (fMRI) studies on the cerebral correlates of speech motor control indicate the "minimal brain network" (Bohland and Guenther 2006) of motor aspects of speech production to encompass, indeed, the anterior insula at the floor of the lateral sulcus, besides mesiofrontal areas, opercular parts of the precentral convolution and/or posterior parts of the inferior frontal gyrus (Broca's area), the "mouth region" of primary sensorimotor cortex, the basal ganglia, and the cerebellar hemispheres (Fig. 2; for a review see Ackermann and Riecker 2010). As a rule, furthermore, functional imaging studies reported left-lateralization effects of hemodynamic activation at the insular level in association with speech motor control processes.

Impact of "motor planning" upon hemodynamic activation of insular cortex

Given that AOS reflects a deficit in the "programming" of vocal tract movements and given that these prearticulatory processes depend upon the anterior insula, any changes in the demands on "motor planning" during speech production must be expected to systematically vary with the BOLD (=blood oxygenation level dependent) responses of intrasylvian cortex. Based upon these suggestions, a more recent fMRI study investigated the impact of utterance length upon hemodynamic activation of the cerebral network of speech motor control (Shuster and Lemieux 2005). Whereas overt (versus silent) repetition of mono- and multisyllabic nouns, indeed, gave rise to activation spots at the floor of the Sylvian fissure, a significant impact of duration could not be detected.

The phonotactic rules, e.g., of the German or English language allow for a variety of syllable onset structures (V, CV, CCV). Besides utterances length, in terms of the number of enclosed syllables, consonant clusters might pose higher demands on articulatory/phonetic control mechanisms as compared to CV units (Aichert and Ziegler 2004). A recent elaborate fMRI study used four tri-syllabic items ("ta-ta-ta"/"ka-ru-ti"/"stra-stra-stra"/"kla-stri-splu"), systematically varied in sequence complexity (the same three versus three different items in a row) and syllabic complexity (CV vs. CCCV onset), as test materials (Bohland and Guenther 2006). Most noteworthy, first, significant left-lateralization effects emerged at the level of intrasylvian cortex, whereas, by contrast, sensorimotor cortex and posterior parts of the inferior frontal gyrus failed to display comparable side-differences of hemodynamic activation. Second, the increase of stimulus complexity in

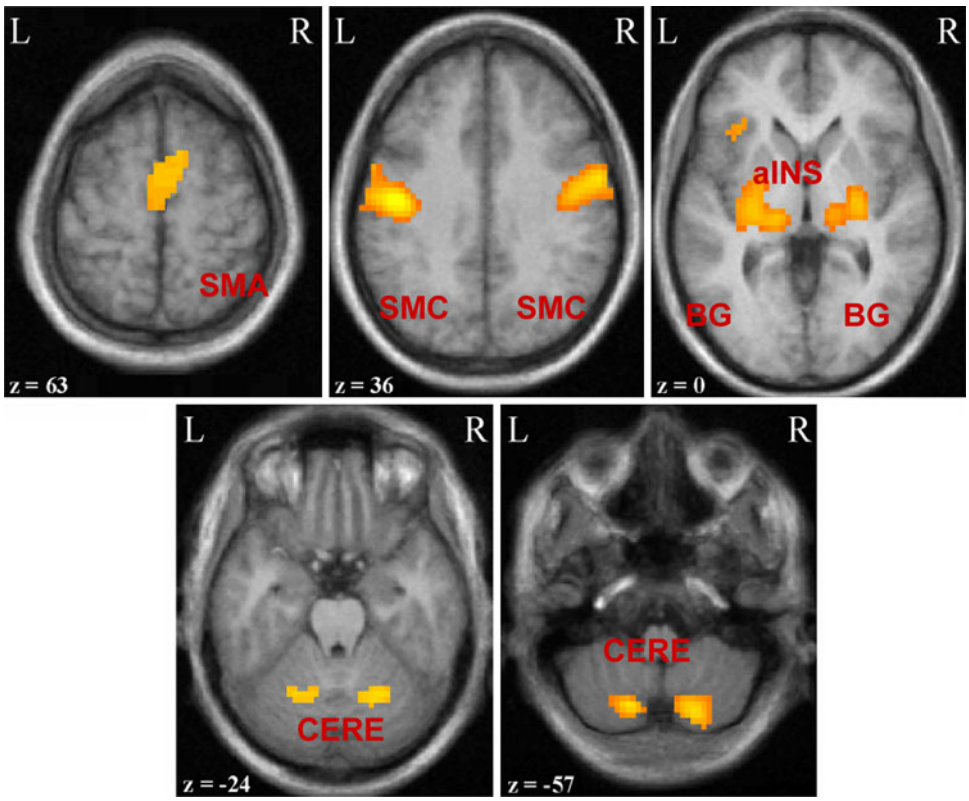

Fig. 2 "Minimal brain network" of speech motor control: fMRI measurements during syllable repetitions (/ta/) at six different frequencies (2.0, 2.5, 3.0, 4.0, 5.0, 6.0 Hz) in normal speakers. The displays show the hemodynamic main effects computed across all six frequency conditions and subjects (*yellow areas*), displayed on transverse sections of the averaged anatomic reference images (*z*,distance to the intercommissural plane; L, left hemisphere, R, right hemisphere). Significant responses emerged within SMA, bilateral sensorimotor cortex (SMC), bilateral basal ganglia (BG), left anterior insula (aINS), left inferior frontal gyrus (not shown), and both cerebellar hemispheres (CERE; from left to right). Analysis of the relationship between syllable frequency and hemodynamic activation revealed positive rate/response functions in all components of the cerebral network of speech motor control, apart from the basal ganglia: Bilateral putamen/pallidum and left caudate nucleus showed, unexpectedly, a negative rate/response function (for further details see Riecker et al. 2005)

either dimension yielded, as expected, enhanced activation of the transition zone between anterior insula and frontoopercular cortex.

The still most elaborated contemporary model of language production (e.g., Levelt et al. 1999) assumes phonetic planning to be centered around the retrieval and assembly of syllable-sized motor programs. Within this conceptual framework, the computational load of higher-order (!) aspects of speech motor control must be expected to vary, in the first instance, with syllable frequency rather than articulatory complexity: The encoding of high-frequency items simply requires access to a "mental syllabary", i.e., a store of highly automatized, pre-compiled, holistic motor routines representing entire syllable structures, whereas syllables of a low frequency of occurrence must be assembled from smaller bits, e.g., from phonemes, a route posing higher demands upon phonetic planning capacities (Cholin et al. 2006). On the basis of this model of language production, experimental variation of syllable frequency, thus, should represent the most adequate probe of phonetic encoding operations. As a consequence, the test materials of a recent fMRI study of our group were systematically controlled for syllable frequency (Riecker et al. 2008). As a second factor, complexity of syllable onset was varied in an orthogonal fashion to the former dimension. A cognitive subtraction approach revealed, in line with the preceding investigation by Bohland and Guenther (2006), a significant main effect of syllable onset complexity (CCV vs. CV), but not the expected impact of syllable frequency (low- vs. high-frequency items) at the level of left-hemisphere posterior inferior frontal gyrus, both cerebellar hemispheres, and the anterior insula. Thus, most noteworthy, intrasylvian cortex seems to be sensitive to the phonetic-linguistic structure of verbal utterances, a strong argument for an engagement of insular cortex in speech motor control processes, in cooperation with ventrolateral frontal areas and, eventually, the cerebellar hemispheres. It should be added that another investigation, based, however, upon less strictly controlled test materials, failed to detect an

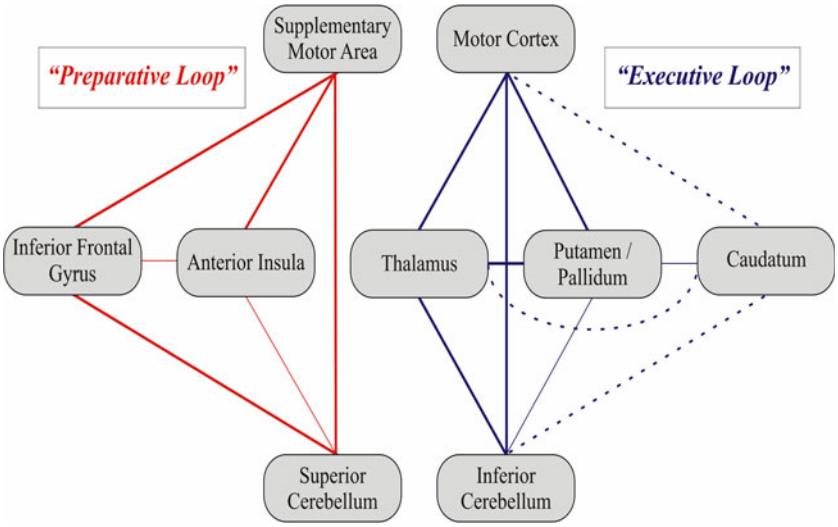

Fig. 3 Quantitative functional connectivity analyses: computed correlation coefficients across the time series of the BOLD (=blood oxygenation level dependent) signal within the volumes of interest considered, i.e., the areas of a significant hemodynamic main effect as displayed in Fig. 2 (*bold lines* = correlation coefficient >0.9, *thin lines* = 0.75–0.9, low and intermediate correlations not depicted; for further details see Riecker et al. 2005)

impact of syllable complexity upon hemodynamic activation of intrasylvian cortex (Sörös et al. 2006).

Besides the production of verbal utterances, there is some evidence for participation of the anterior insula in speech-related perceptual functions. Thus, fMRI measurements during application (passive listening task) of isochronous synthetic click trains or syllable repetitions (range 2–6 Hz) revealed hemodynamic insular activation to depend upon presentation rate (Ackermann et al. 2001; Steinbrink et al. 2009). More specifically, BOLD responses increased/decreased at the left/right side as a function of click frequency and, thus, resembled high-pass (left side) or low-pass filtered (right side) signal series. By contrast to healthy controls, the anterior insula, first, failed to display these rate/response profiles and, second, showed reduced hemodynamic activation under both the speech and non-speech conditions in subjects with developmental dyslexia (Steinbrink et al. 2009). Apparently, thus, the rostral insular is engaged in the temporal processing of auditory stimuli.

Temporal dynamics of hemodynamic responses of intrasylvian cortex

The assumption that the anterior insula closely cooperates with ventrolateral frontal cortex during speech production is further corroborated by two fMRI studies of our group which analyzed the temporal dynamics of the BOLD signal changes during syllable repetitions. First, functional connectivity analysis, based upon the temporal dynamics of hemodynamic activation, revealed a segregation of the cerebral structures engaged in speech motor control into two clusters: SMA, Broca's area, anterior insula, and superior cerebellum, on the one hand, and sensorimotor cortex, thalamus, basal ganglia, inferior cerebellum, on the other hand, were found to be interconnected each by high (0.75–0.9) and very high (>0.9) correlation coefficients (Fig. 3; Riecker et al. 2005). A subsequent investigation calculated the time course of the hemodynamic responses prior and during forewarned syllable repetitions (Brendel et al. 2010). In line with those findings, Broca's area and anterior insula showed the same temporal profile of hemodynamic activation with a significantly earlier peak than the response of sensorimotor cortex.

Summary

At the cytoarchitectural level, the insular cortex both of Old World monkeys and our own species can be subdivided along the rostrocaudal axis into an agranular, a dysgranular, and a granular zone (Mesulam and Mufson 1982). The agranular and the rostral dysgranular areas represent, concomitant with the adjacent orbitofrontal and temporopolar regions, a link between allo- and isocortex, hence the designation "paralimbic" structures. It is a bit bewildering that motor capacities unique to our species might depend along with swallowing upon paralimbic components of the brain. Nevertheless, a survey of the relevant functional imaging studies revealed, by and large, consistent activation of insular cortex—predominantly, but not exclusively, within the language-dominant hemisphere—during tasks addressing motor aspects of speech production. The sensitivity to phonetic-linguistic complexity of verbal utterances represents so far the strongest evidence for a specific engagement of the floor of the Sylvian fissure in the control of (higher-order) articulatory processes. Most noteworthy, the fMRI study by Bohland and Guenther (2006) found the relevant response located at the junction to the frontal operculum at either side. There is, however, no one-to-one correlation between surface markers of the brain, e.g., the salient angular transition from the intrasylvian part of the frontal operculum to the

floor of the lateral sulcus, and the functionally relevant cytoarchitectural compartmentalization of the cortex. For example, the macroscopic contours of the posterior part of the inferior frontal gyrus do not reliably coincide with the borders of BA 44 and 45 (Amunts et al. 1999). It cannot be excluded, therefore, that the intrasylvian hemodynamic activation spot, engaged in higher-order aspects of speech motor control, is continuous at the level of microscopic structure with the opercular part of the inferior frontal gyrus, representing just the most ventromedial part of a more extensive anterior perisylvian area of speech motor control (see Figs. 4 and 5 in Bohland and Guenther 2006). In some support for this assumption, the severity of AOS has been found correlated with lesion size across both insular cortex and adjacent fronto-opercular areas (Ogar et al. 2006).

The impact of intrasylvian cortex upon autonomic aspects of speech motor control (regulation of respiratory activity)

Besides the insular-opercular transition zone, functional imaging studies point, however, at a further distinct separate response within the precentral intrasylvian gyrus (Bohland and Guenther 2006) or at a more extensive pattern of rostro-insular hemodynamic activation (Riecker et al. 2008) during speech production. In addition, BOLD signal changes of the posterior insula have been reported in association with productions of the vowel/a:/(Sörös et al. 2006). So, the question arises whether and in how far the insula supports more speech-relevant functions than just higher-order articulatory processes. Both experimental and clinical data indicate intrasylvian cortex to be engaged in the regulation of autonomic functions such as the cardiovascular system and glucose metabolism. For example, electrical stimulation at the floor of the Sylvian fissure in subhuman primates (Wall and Davis 1951) as well as our species (Oppenheimer et al. 1992) was found frequently to elicit changes in heart rate and blood pressure. And insular infarctions—presumably, at either side of the brain—may elicit abnormalities of heart rate or myocardial injury (Christensen et al. 2005; Ay et al. 2006; Laowattana et al. 2006). At least in cerbrovascular disorders, a release of inhibitory effects upon sympathoexcitatory forebrain structures, e.g., the hypothalamus, and brainstem nuclei appears to represent a major pathomechanism of insular autonomic effects (Sander et al. 2001). This impact of intrasylvian cortex upon, especially, sympathetic tone could explain why hemoynamic activation of intrasylvian cortex represents a widespread finding across many different experimental conditions besides spoken language. For example, tasks involving positive and affiliative feelings such as maternal or romantic love, attention to pleasant music or happy voices, and the experience of joy engage predominantly or even exclusively left-hemisphere anterior insula (Craig 2009). In addition, the ipsilateral intrasylvian cortex has also been found to respond to uncomfortable experiences such as unpleasant odors, concomitant with increased autonomic arousal in terms of electrodermal reactions (e.g., Royet et al. 2003). And both the feeling of disgust and the observation of the respective facial expression in others were found to yield an overlapping hemodynamic response within left anterior insula (Wicker et al. 2003). Besides a distinct contribution to spoken language at the level of the insulo-opercular junction, further separate responses of paralimbic intrasylvian cortex just could reflect, as a highly conservative interpretation, unspecific autonomic arousal due to, e.g., the attentional demands imposed by the experiments on the subjects.

As an alternative, speech production might be associated with more domain-specific aspects of autonomic functions. Although spoken language represents a unique capacity of our species, inaccessible even to our closest primate relatives (Wallman 1992), speech motor control must by virtue of its link to respiratory activity interact with the phylogenetically older autonomic system. In subhuman primates, small-diameter afferent fibers which "sense" the actual mechanical and metabolic conditions of all the tissues of an organism project ultimately—via lamina I of the spinal or trigemina doral horn and the posterior part of the ventromedial thalamic nucleus—to the posterior intrasylvian cortex at either side of the brain (Craig 2002, 2003). Together with input from similar fibers of the cranial, especially the glossopharyngeal and vagal nerves, relayed to the nucleus of the solitary tract and then to the basal part of the ventromedial nucleus of the thalamus, this hierarchical afferent system creates a sensory "image" of interoceptive information within the posterior insula, encoding the physiological condition of the entire body at the cortical level. Based upon functional imaging studies, this map could be assigned in humans, more specifically, to the superior limiting sulcus of caudal intrasylvian cortex. Subsequent sequential re-coding ("post-processing") of these data, evolving across mid-intrasylvian cortex, anterior insula and orbitofrontal cortex, then seems to provide the basis, at least in our species, for the subjective evaluation of interoceptive input (Craig 2009). Respiration-related information also seems to be transmitted to and evaluated within the intrasylvian cortex. Thus, a PET study found dyspnea (breathlessness, shortness of breath, air hunger) to elicit bilateral, but predominantly right-lateralized hemodynatmic activation of mid/anterior insula (Banzett et al. 2000). More or less, the selected experimental design models the situation of a patient who cannot "inspire deeply enough due to impaired lungs or

respiratory muscles". The strong feelings of discomfort under these conditions could explain the mid/anterior rather than posterior location of the evoked hemodynamic insular responses. Nevertheless, the model of an exhaustive posterior-insular representation of the mechanical and metabolic state of the various body tissues could explain why, especially, the production of a the isolated vowel "ah" yielded, among others, bilateral hemodynamic activation (versus a rest condition) of the caudal, but not rostral part of intrasylvian cortex (Sörös et al. 2006). Under these conditions, monitoring of respiration-related enteroceptive states might provide important information to the speaker, e.g., as a prerequisite to smooth control of voluntary exhalation.

Besides their projections to the thalamus and the cortex, the neurons of the spinal/trigeminal dorsal horn as well as the tractus solitarius feed into brainstem "somato-autonomic reflex arcs", engaged in the maintenance of body homeostasis. This network allows an organism to "respond in an integrated and ongoing fashion to interior and exterior environmental challenges, ranging from exercise, dehydration or altitude to injury, sepsis or social interactions" (Craig 2002, p. 664). Brainstem mechanisms, acting upon respiratory neural pacemakers and pattern generators, also regulate arterial blood gas status in response to alterations in airflow resistance as well as metabolic and biomechanical conditions, e.g., changes in posture ("automatic control of breathing"; Shea 1996). In addition, our species is capable of highly precise voluntary control of respiratory activities via corticospinal and parallel corticobulbar pathways ("voluntary control of breathing"), e.g., during vocal and instrumental musical performance. Furthermore, this control system should be active during clinical tests such as maximum performance tasks (sustained vowels "as long as possible") since the brainstem reflexes counteracting deterioration of blood gas status and experienced dyspnea must be overridden under these conditions.

In addition to the cardiovascular system, neurophysiological data indicate that the insula also engages in the active control of respiration. Electrical stimulation of the anterior insula in rhesus macaques has been found to cause "respiratory slowing" and, finally, "arrest in expiration" (Sugar et al. 1948), and these effects persisted after bilateral section of the vagus nerves (Hoffman and Rasmussen 1953). This respiration-related area extends, among others, to the adjacent orbital surface of the frontal lobe in rostral direction ("partial or complete inhibition of respiratory movements"; Kaada et al. 1949). Comparable observations have been made in human subjects undergoing surgery for medically untractable seizures ("depression of respiration"; Penfield and Faulk 1955; but see Oppenheimer et al. 1992). However, signs of compromised speech breathing do not pertain to the clinical profile of AOS (Duffy 2005) and also have not reported in subjects suffering from uni- or bilateral insular pathology. Since, however, insular representation of autonomic functions, most presumably, lacks strict lateralization effects, compensation via the other hemisphere might have taken place in these instances. Conceivably, insular fiber tracts operate as a corollary and supportive control system in parallel to corticobulbar and spinal projections. Whereas the projections of primary and premotor cortex, presumably, transmit phasic control signals, responsible for rapid or brief adjustments of respiratory activity to linguistic demands or linguistic constraints such as breath-taking at sentence boundaries, intrasylvian cortex might be instrumental in more "tonic" aspects of respiratory control. For example, subjects hyperventilate when they speak at rest since the mean flow requirements exceed resting ventilation under these conditions (Shea 1996). Such task-related adaptive settings could well be under the control of the insular-autonomic system, e.g., via inhibition of the "depressive" impact of intrasylvian cortex upon ventilatory drive.

Conclusions

It is well established that damage to the ventrolateral left-hemisphere frontal lobe, i.e., posterior parts of the inferior frontal gyrus (Broca's area) and/or the lower (opercular) precentral convolution, may give rise to the distinct articulatory/phonatory deficits of AOS, reflecting allegedly disrupted higher-order aspects of speech motor control. By contrast, such deficits were less frequently and less reliably observed in patients with more or less isolated insular infarction or a brain tumor restricted to the floor of the Sylvian fissure. And the results of electrical cortical stimulation of these structures prior to or during brain surgery are also less conclusive. More recent functional imaging data suggest, however, a specific contribution of the rostral insula—a region adjacent to the junction to fronto-opercular cortex—to motor aspects of spoken language. The relatively small extent of the relevant area could explain the rather sparse observations of intrasylvian AOS.

Functional imaging data also indicate that the intrasylvian hemodynamic responses during speech motor control tasks exceed beyond articulation-related activities. Since (most) speech sounds of the various human languages arise from specific modulations of the expiratory air stream at the laryngeal and supralaryngeal level, spoken language must be inherently linked to the control of respiratory activity. First, there is evidence that posterior insular cortex is engaged in the representation of interoceptive states and, thus, might operate as a relay station for the transmission of speech-relevant information on respiration-related

metabolic states. This input might be highly relevant in situations requiring speech production to override experienced dyspnea. Second, the rostral paralimbic insular seems to participate, among others, in the efferent control of respiration. Conceivably, insular projections to the cerebral "centers" of the autonomic system mediate a domain-specific presetting of vegetative functions such as the maintenance of a state of hyperventilation during speech production. The insula, thus, might operate as a corollary pathway to the efferent fiber tracts of primary motor and premotor ventrolateral frontal areas engaged in the "voluntary control of breathing". In line with these suggestions, only motor functions bound to upper midline structures—speech production, non-speech orofacial gestures, swallowing—appear to be associated with intrasylvian cortex, i.e., movement sequences bound to upper midline structures also engaged in feeding and respiration. And these activities are at least partially under the influence of the autonomic system and, therefore, require the adjustment of voluntary and autonomic activities.

References

Ackermann H, Riecker A (2004) The contribution of the insula to motor aspects of speech production: a review and a hypothesis. Brain Lang 89:320–328

Ackermann H, Riecker A (2010) Cerebral control of motor aspects of speech production: neurophysiological and functional imaging data. In: Maassen B, van Lieshout PHHM (eds) Speech motor control: new developments in basic and applied research. Oxford University Press, Oxford, pp 117–134

Ackermann H, Ziegler W (2010) Brain mechanisms underlying speech motor control. In: Hardcastle WJ, Laver J, Gibbon FE (eds) The handbook of phonetic sciences, 2nd edn. Wiley-Blackwell, Malden, pp 202–250

Ackermann H, Daum I, Schugens MM, Grodd W (1996) Impaired procedural learning after damage to the left supplementary motor area (SMA). J Neurol Neurosurg Psychiatry 60:94–97

Ackermann H, Riecker A, Mathiak K, Erb M, Grodd W, Wildgruber D (2001) Rate-dependent activation of a prefrontal-insular-cerebellar network during passive listening to trains of click stimuli: an fMRI study. NeuroReport 12:4087–4092

Ackermann H, Riecker A, Wildgruber D (2004) Functional brain imaging of motor aspects of speech production. In: Maassen B, Kent RD, Peters HFM, van Lieshout PHHM, Hulstijn W (eds) Speech motor control in normal and disordered speech. Oxford University Press, Oxford, pp 85–111

Ackermann H, Mathiak K, Riecker A (2007) The contribution of the cerebellum to speech production and speech perception: clinical and functional imaging data. Cerebellum 6:202–213

Ackermann H, Hertrich I, Ziegler W (2010) Dysarthria. In: Damico JS, Müller N, Ball MJ (eds) The handbook of language and speech disorders. Wiley-Blackwell, Malden, pp 362–390

Aichert I, Ziegler W (2004) Syllable frequency and syllable structure in apraxia of speech. Brain Lang 88:148–159

Alexander MP, Naeser MA, Palumbo CL (1987) Correlations of subcortical CT lesion sites and aphasia profiles. Brain 110:961–991

Alexander MP, Benson DF, Stuss DT (1989) Frontal lobes and language. Brain Lang 37:656–691

Allport LE, Butcher KS, Baird TA, MacGregor L, Desmond PM, Tress BM, Colman P, Davis SM (2004) Insular cortical ischemia is independently associated with acute stress hyperglycemia. Stroke 35:1886–1891

Amunts K, Schleicher A, Bürgel U, Mohlberg H, Uylings HB, Zilles K (1999) Broca's region revisited: cytoarchitecture and intersubject variability. J Comp Neurol 412:319–341

Ardila A, Benson DF, Flynn FG (1997) Participation of the insula in language. Aphasiology 11:1159–1169

Augustine JR (1985) The insular lobe in primates including humans. Neurol Res 7:2–10

Augustine JR (1996) Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Brain Res Rev 22:229–244

Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, Ayata C, Zhu M, Schwamm LH, Sorensen AG (2006) Neuroanatomic correlates of stroke-related myocardial injury. Neurology 66:1325–1329

Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJS, Adams L (2000) Breathlessness in humans activates insular cortex. Neuroreport 11:2117–2120

Bass AH, Gilland EH, Baker R (2008) Evolutionary origins for social vocalization in a vertebrate hindbrain-spinal compartment. Science 321:417–421

Benson DF, Sheremata WA, Bouchard R, Segarra JM, Price D, Geschwind N (1973) Conduction aphasia: a clinicopathological study. Arch Neurol 28:339–346

Bohland JW, Guenther FH (2006) An fMRI investigation of syllable sequence production. Neuroimage 32:821–841

Botez MI, Barbeau A (1971) Role of subcortical structures, and particularly of the thalamus, in the mechanisms of speech and language: a review. Int J Neurol 8:300–320

Brendel B, Hertrich I, Erb M, Lindner A, Riecker A, Grodd W, Ackermann H (2010) The contribution of mesiofrontal cortex to the preparation and execution of repetitive syllable productions: an fMRI study. Neuroimage 50:1219–1230

Broca P (1861) Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). Bull de la Société Anatomique de Paris 36:330–357

Broca P (1865) Du siège de la faculté du langage articulé dans l'hémisphère gauche du cerveau. Bull de la Société d'Anthropologie de Paris 6:377–393

Brooks VB (1986) The neural basis of motor control. Oxford University Press, New York

Cancelliere AEB, Kertesz A (1990) Lesion localization in acquired deficits of emotional expression and comprehension. Brain Cogn 13:133–147

Caplan D (1987) Neurolinguistics and linguistic aphasiology: an introduction. Cambridge University Press, Cambridge

Cereda C, Ghika J, Maeder P, Bogousslavsky J (2002) Strokes restricted to the insular cortex. Neurology 59:1950–1955

Cholin J, Levelt WJM, Schiller N (2006) Effects of syllable frequency in speech production. Cognition 99:205–235

Christensen H, Boysen G, Christensen AF, Johannesen HH (2005) Insular lesions, ECG abnormalities, and outcome in acute stroke. J Neurol Neurosurg Psychiatry 76:269–271

Colivicchi F, Bassi A, Santini M, Caltagirone C (2005) Prognostic implications of right-sided insular damage, cardiac autonomic derangement, and arrhythmias after acute ischemic stroke. Stroke 36:1710–1715

Craig AD (2002) How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3:655–666

Craig AD (2003) Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 13:500–505

Craig AD (2009) How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci 10:59–70
Damasio H, Damasio AR (1980) The anatomical basis of conduction aphasia. Brain 103:337–350
Daniels SK, Foundas AL (1997) The role of the insular cortex in dysphagia. Dysphagia 12:146–156
Dronkers NF (1996) A new brain region for coordinating speech articulation. Nature 384:159–161
Duffau H, Capelle L, Lopes M, Faillot T, Sichez JP, Fohanno D (2000) The insular lobe: physiopathological and surgical considerations. Neurosurgery 47:801–810
Duffau H, Bauchet L, Lehéricy S, Capelle L (2001) Functional compensation of the left dominant insula for language. Neuroreport 12:2159–2163
Duffy JR (2005) Motor speech disorders: substrates, differential diagnosis, and management, 2nd edn. Elsevier Mosby, St. Louis
Ebeling U, Kothbauer K (1995) Circumscribed low grade astrocytomas in the dominant opercular and insular region: a pilot study. Acta Neurochir (Wien) 132:66–74
Eickhoff SB, Weiss PH, Amunts K, Fink GR, Zilles K (2006) Identifying human parieto-insular vestibular cortex using fMRI and cytoarchitectonic mapping. Hum Brain Mapp 27:611–621
Etgen T, Winbeck K, Conrad B, Sander D (2003) Hemiballism with insular infarction as first manifestation of Takayasu's arteritis in association with chronic hepatitis B. J Neurol 250:226–229
Fink JN, Selim MH, Kumar S, Voetsch B, Fong WC, Caplan LR (2005) Insular cortex infarction in acute middle cerebral artery territory stroke. Arch Neurol 62:1081–1085
Fox PT, Huang A, Parsons LM, Xiong JH, Zamarippa F, Rainey L, Lancaster JL (2001) Location-probability profiles for the mouth region of human primary motor-sensory cortex: model and validation. Neuroimage 13:196–209
Freedman M, Alexander MP, Naeser MA (1984) Anatomic basis of transcortical motor aphasia. Neurology 34:409–417
Geschwind N (1965) Disconnexion syndromes in animals and man. Brain 88(237–294):585–644
Goldstein K (1911) Über die amnestische und zentrale Aphasie. Arch Psychiat Neurol 48:408–458
Goldstein K (1948) Language and language disturbances: aphasic symptom complexes and their significance for medicine and theory of language. Grune & Stratton, New York
Griffiths TD, Warren JD, Dean JL, Howard D (2004) "When the feeling's gone": a selective loss of musical emotion. J Neurol Neurosurg Psychiatry 75:344–345
Habib M, Daquin G, Milandre L, Royere ML, Rey M, Lanteri A, Salamon G, Khalil R (1995) Mutism and auditory agnosia due to bilateral insular damage: role of the insula in human communication. Neuropsychologia 33:327–339
Hage SR, Jürgens U (2006) On the role of the pontine brainstem in vocal pattern generation: a telemetric single-unit recording study in the squirrel monkey. J Neurosci 26:7105–7115
Hécaen H, Consoli S (1973) Analyse des troubles du langage au cours des lésions de l'aire de Broca. Neuropsychologia 11:377–388
Henderson VW (1992) Early concepts of conduction aphasia. In: Kohn SE (ed) Conduction aphasia. Lawrence Erlbaum Associates, Hillsdale, pp 23–38
Hillis AE, Work M, Barker PB, Jacobs MA, Breese EL, Maurer K (2004) Re-examining the brain regions crucial for orchestrating speech articulation. Brain 127:1479–1487
Hoffman BL, Rasmussen T (1953) Stimulation studies of insular cortex of *Macaca mulatta*. J Neurophysiol 16:343–351
Jürgens U (2002) Neural pathways underlying vocal control. Neurosci Biobehav Rev 26:235–258
Jürgens U, von Cramon D (1982) On the role of the anterior cingulate cortex in phonation: a case report. Brain Lang 15:234–248
Kaada BR, Pribram KH, Epstein JA (1949) Respiratory and vascular responses in monkeys from temporal pole, insula, orbital surface and cingulate gyrus. J Neurophysiol 12:347–356
Kent RD (1997) The speech sciences. Singular, San Diego
Kreisler A, Godefroy O, Delmaire C, Debachy B, Leclercq M, Pruvo JP, Leys D (2000) The anatomy of aphasia revisited. Neurology 54:1117–1123
Kumabe T, Nakasato N, Suzuki K, Sato K, Sonoda Y, Kawagishi J, Yoshimoto T (1998) Two-staged resection of a left frontal astrocytoma involving the operculum and insula using intraoperative neurophysiological monitoring: case report. Neurol Med Chir (Tokyo) 38:503–507
Lang FF, Olansen NE, De Monte F, Gokaslan ZL, Holland EC, Kalhorn C, Sawaya R (2001) Surgical resection of intrinsic insular tumors: complication avoidance. J Neurosurg 95:638–650
Laowattana S, Zeger SL, Lima JAC, Goodman SN, Wittstein LS, Oppenheimer SM (2006) Left insular stroke is associated with adverse cardiac outcome. Neurology 66:477–483
Levelt WJM, Roelofs A, Meyer AS (1999) A theory of lexical access in speech production. Behav Brain Sci 22:1–75
Lichtheim L (1885) On aphasia. Brain 7:443–484
Mao CC, Coull BM, Golper LA, Rau MT (1989) Anterior operculum syndrome. Neurology 39:1169–1172
Marien P, Pickut BA, Engelborghs S, Martin JJ, De Deyn PP (2001) Phonological agraphia following a focal anterior insulo-opercular infarction. Neuropsychologia 39:845–855
Mazzocchi F, Vignolo LA (1979) Localisation of lesions in aphasia: clinical-CT scan correlations in stroke patients. Cortex 15:627–653
McNeil MR, Robin DA, Schmidt RA (1997) Apraxia of speech: definition, differentiation, and treatment. In: McNeil MR (ed) Clinical management of sensorimotor speech disorders. Thieme, New York, pp 311–344
Mesulam MM, Mufson EJ (1982) Insula of the old world monkey. I: architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol 212:1–22
Mohr JP, Pessin MS, Finkelstein S, Funkenstein HH, Duncan GW, Davis KR (1978) Broca aphasia: pathologic and clinical. Neurology 28:311–324
Murdoch BE, Thompson EC, Theodoros DG (1997) Spastic dysarthria. In: McNeil MR (ed) Clinical management of sensorimotor speech disorders. Thieme, New York, pp 287–310
Nagao M, Takeda K, Komori T, Isozaki E, Hirai S (1999) Apraxia of speech associated with an infarct in the precentral gyrus of the insula. Neuroradiology 41:356–357
Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR (2003) Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. Brain 126:2406–2418
Ogar J, Slama H, Dronkers N, Amici S, Gorno-Tempini ML (2005) Apraxia of speech: an overview. Neurocase 11:427–432
Ogar J, Willock S, Baldo J, Wilkins D, Ludy C, Dronkers N (2006) Brain Lang 97:343–350
Ojemann GA (1994) Cortical stimulation and recording in language. In: Kertesz A (ed) Localization and neuroimaging in neuropsychology. Academic Press, San Diego, pp 35–55
Ojemann GA, Whitaker HA (1978) Language localization and variability. Brain Lang 6:239–260
Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC (1992) Cardiovascular effects of human insular cortex stimulation. Neurology 42:1727–1732
Ostrowsky K, Isnard J, Ryvlin P, Guénot M, Fischer C, Mauguière F (2000) Functional mapping of the insular cortex: clinical implication in temporal lobe epilepsy. Epilepsia 41:681–686

Penfield W, Faulk ME (1955) The insula: further observations on its function. Brain 78:445–470
Penfield W, Roberts L (1959) Speech and brain-mechanisms. Princeton University Press, Princeton
Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME (1988) Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 331:585–589
Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME (1989) Positron emission tomographic studies of the processing of single words. J Cogn Neurosci 1:153–170
Riecker A, Mathiak K, Wildgruber D, Erb M, Hertrich I, Grodd W, Ackermann H (2005) fMRI reveals two distinct cerebral networks subserving speech motor control. Neurology 64:700–706
Riecker A, Brendel B, Ziegler W, Erb M, Ackermann H (2008) The influence of syllable onset complexity and syllable frequency on speech motor control. Brain Lang 107:102–113
Riecker A, Gastl R, Kühnlein P, Kassubek J, Prosiegel M (2009) Dysphagia due to unilateral infarction in the vascular territory of the anterior insula. Dysphagia 24:114–118
Rizzolatti G, Sinigaglia C (2006) Mirrors in the brain: how our minds share actions and emotions. Oxford University Press, Oxford
Royet JP, Plailly J, Delon-Martin C, Kareken DA, Segebarth C (2003) FMRI of emotional responses to odors: influence of hedonic valence and judgment, handedness, and gender. Neuroimage 20:713–728
Rubens AB (1975) Aphasia with infarction in the territory of the anterior cerebral artery. Cortex 11:239–250
Sander D, Winbeck K, Klingelhöfer J, Etgen T, Conrad B (2001) Prognostic relevance of pathological sympathetic activation after acute thromboembolic stroke. Neurology 57:833–838
Schiff HB, Alexander MP, Naeser MA, Galaburda AM (1983) Aphemia: clinical-anatomic correlations. Arch Neurol 40:720–727
Schneider RC, Calhoun HD, Kooi KA (1971) Circling and rotational automatisms in patients with frontotemporal cortical and subcortical lesions. J Neurosurg 35:554–563
Shea SA (1996) Behavioural and arousal-related influences on breathing in humans. Exp Physiol 81:1–26
Shuren J (1993) Insula and aphasia. J Neurol 240:216–218
Shuster LI, Lemieux SK (2005) An fMRI investigation of covertly and overtly produced mono- and multisyllabic words. Brain Lang 93:20–31
Sidiropoulos K, de Bleser R, Ackermann H, Preilowski B (2008) Prelexical disorders in repetition conduction aphasia. Neuropsychologia 46:3225–3238
Sörös P, Sokoloff LG, Bose A, McIntosh AR, Graham SJ, Stuss DT (2006) Clustered functional MRI of overt speech production. Neuroimage 32:376–387
Starkstein SE, Berthier M, Leiguarda R (1988) Bilateral opercular syndrome and crossed aphemia due to a right insular lesion: a clinicopathological study. Brain Lang 34:253–261
Steinbrink C, Ackermann H, Lachmann T, Riecker A (2009) Contribution of the anterior insula to temporal auditory processing deficits in developmental dyslexia. Hum Brain Mapp 30:2401–2411
Sugar O, Chusid JG, French JD (1948) A second motor cortex in the monkey (*Macaca mulatta*). J Comp Neurol 7:182–189
Thiel A, Herholz K, Koyuncu A, Ghaemi M, Kracht LW, Habedank B, Heiss WD (2001) Plasticity of language networks in patients with brain tumors: a positron emission tomography activation study. Ann Neurol 50:620–629
Voets NL, Adcock JE, Flitney DE, Behrens TEJ, Hart Y, Stacey R, Carpenter K, Matthews PM (2006) Distinct right frontal lobe activation in language processing following left hemisphere injury. Brain 129:754–766
Wall PD, Davis GD (1951) Three cerebral cortical systems affecting autonomic function. J Neurophysiol 14:507–517
Wallman J (1992) Aping language. Cambridge University Press, Cambridge
Wernicke C (1874) Der aphasische symptomencomplex: eine psychologische Studie auf anatomischer Basis. Cohn & Weigert, Breslau
Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G (2003) Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. Neuron 40:655–664
Wise RJS, Greene J, Büchel C, Scott SK (1999) Brain regions involved in articulation. Lancet 353:1057–1061
Yasargil MG, von Ammon K, Cavazos E, Doczi T, Reeves JD, Roth P (1992) Tumours of the limbic and paralimbic systems. Acta Neurochir (Wien) 118:40–52
Zentner J, Meyer B, Stangl A, Schramm J (1996) Intrinsic tumors of the insula: a prospective surgical study of 30 patients. J Neurosurg 85:263–271
Ziegler W (2008) Apraxia of speech. In: Goldenberg G, Miller B (eds) Handbook of clinical neurology, vol 88 (3rd series). Elsevier, London, pp 269–285
Ziegler W, Kilian B, Deger K (1997) The role of the left mesial frontal cortex in fluent speech: evidence from a case of left supplementary motor area hemorrhage. Neuropsychologia 35:1197–1208