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Frontal-thalamic circuits associated with language

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ABSTRACT

Thalamic nuclei associated with language including the ventral lateral, ventral anterior, intralaminar and mediodorsal form a hub that uniquely receives the output of the basal ganglia and cerebellum, and is connected with frontal (premotor and prefrontal) cortices through two parallel circuits: a thalamic pathway targets the middle frontal cortical layers focally, and the other innervates widely cortical layer 1, poised to recruit other cortices and thalamic nuclei for complex cognitive operations. Return frontal pathways to the thalamus originate from cortical layers 6 and 5. Information through this integrated thalamo-cortical system is gated by the inhibitory thalamic reticular nucleus and modulated by dopamine, representing a specialization in primates. The intricate dialogue of distinct thalamic nuclei with the basal ganglia, cerebellum, and specific dorsolateral prefrontal and premotor cortices associated with language, suggests synergistic roles in the complex but seemingly effortless sequential transformation of cognitive operations for speech production in humans.

1. Overview: distributed neural circuits associated with language

The complex neural processing for language involves a large number of cortical areas and subcortical structures. Among the latter, damage to ventral lateral (VL), ventral anterior (VA), intralaminar, and mediodorsal (MD) thalamic nuclei consistently leads to language disturbances. This review centers on these thalamic nuclei which serve as a hub to link three structures associated with language: the frontal cortex, the basal ganglia and the cerebellum. Thalamic nuclei associated with language processes receive the output of the basal ganglia and the cerebellum and have bidirectional connections with the frontal cortex. As summarized in Fig. 1, the focus here is on the anatomic organization of this integrated circuit, its monitoring by a fast and early processing inhibitory system mediated by the thalamic reticular nucleus (TRN), and modulation by dopamine, whose precise regulation is essential for cognitive operations [reviewed in Arnsten and Li (2005)].

The term frontal cortex refers to the large cortical expanse that includes the motor cortex at its posterior extent, and progressively more anteriorly the premotor and prefrontal cortices (Figs. 1 and 2). The lateral frontal cortex includes Broca's region, which is associated with language. On the other hand, damage to prefrontal areas does not lead to aphasia, but based on the role of prefrontal areas in sequencing information in working memory, their integrity is essential for fluent speech.

Classical neuropathological and modern imaging studies have also associated several post-Rolandic areas with language. Among these, temporal auditory areas that process sound stimuli project to frontal areas for speech articulation in areas 44/45 (Hickok & Poeppel, 2004) which make up Broca's region on the left hemisphere, as well as to prefrontal areas 46 and 9, which are associated with working memory [reviewed in Saur et al. (2008) and Petrides and Pandya (2009)]. Post-Rolandic parietal and temporal cortices associated with language on the left side include Wernicke's areas, which are thought to process meaningful speech [reviewed in Galaburda, LeMay, Kemper, and Geschwind (1978), Toga and Thompson (2003), Hickok and Poeppel (2004, 2007), Stowe, Haverkort, and Zwarts (2005), Bennett and Hacker (2006) and Price (2010)]. These parieto-temporal cortices are connected with the lateral posterior and pulvinar thalamic nuclei, which project widely to other cortices as well, including some occipital and prefrontal cortices [reviewed in Jones (2007)]. There is some evidence that damage to the pulvinar or lateral posterior nuclei also results in language disturbances (Crosson, 1999). This review is based only on thalamic nuclei associated with premotor and prefrontal cortices whose damage results in severe language disturbances. The focus is on the frontal cortical connections of these thalamic nuclei, and their relationship with the basal ganglia and distinct cerebellar sites associated with language. This review does not consider the

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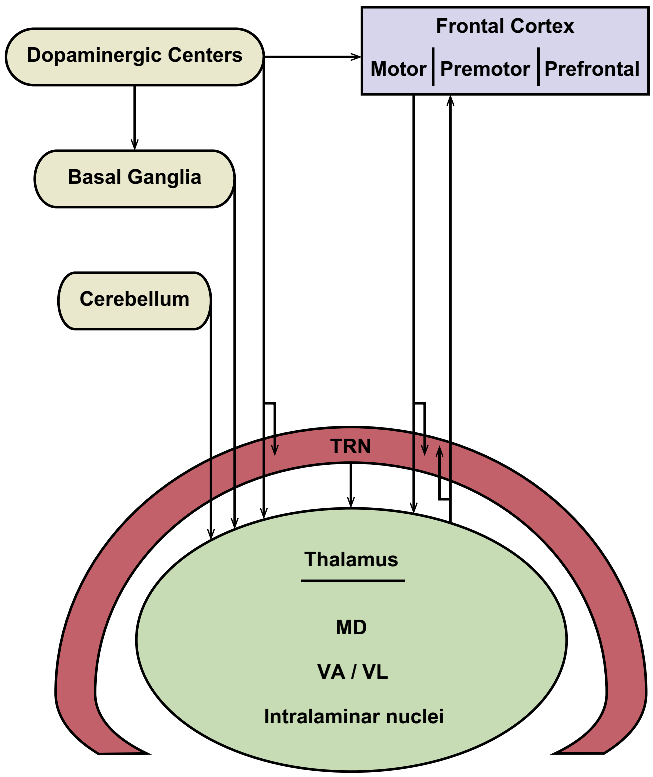

Fig. 1. Thalamic nuclei that serve as a hub for distributed neural circuits associated with language. The nodes of networks that interact with the thalamus include: the frontal cortex, which consists of motor, premotor, and prefrontal areas; basal ganglia; cerebellum; dopaminergic groups from the mesencephalic substantia nigra *pars compacta* and the ventral tegmental area; and the inhibitory thalamic reticular nucleus (TRN). Thalamic nuclei: MD, mediodorsal; VA, ventral anterior; VL, ventral lateral.

various theories about language processing in the brain, or describe the large number of post-Rolandic cortices that have been associated with specific linguistic tasks in functional imaging studies. Temporal, parietal and occipital cortices have topographic connections with prefrontal and premotor cortices, as described elsewhere [e.g., (Barbas, 1992, 2000a; Barbas, Ghashghaei, Rempel-Clower, & Xiao, 2002)].

2. Frontal cortices and language

Lateral areas 44 and 45 in the human brain are situated within the frontal language region of Broca and have a direct role in speech production. Area 44 is engaged also during silent speech (Friedman et al., 1998; Grafton, Fadiga, Arbib, & Rizzolatti, 1997). In the rhesus monkey brain area 44 lies within the premotor region and area 45 is located rostrally in the adjacent prefrontal cortex (Fig. 2A and B). Other premotor cortices include area 6, which is found behind and largely dorsal to areas 44 and 45. At its most dorsal extent area 6 gives way to the supplementary motor area (SMA), which extends to the medial surface. The SMA is situated within the dorsal and medial part of area 6 in Brodmann's map (Brodmann, 1905; reviewed in Chouinard & Paus, 2006; Dum & Strick, 2002). On the medial surface, the cingulate motor areas are located on the cingulate gyrus below the SMA (or area 6 in Fig. 2, top). The pre-SMA is found anterior to the SMA on the medial and dorsal surface. Areas found below and anterior to the medial premotor cortices include the anterior cingulate cortex (ACC). The ACC has an important role in vocalization within an emotional context (Barbas, 2000b), and a key role in allocating attentional resources, both of which are important processes for language.

Situated in front and above lateral areas 44 and 45, dorsolateral prefrontal areas 46 and 9 have synergistic roles in cognitive processes and are engaged in language functions that require holding information within working memory. Areas 46, 9, and the ACC have strong connections with neighboring premotor cortices, and especially its dorsal and medial sectors via corticocortical connections, as well as through common nuclei in the thalamus [reviewed in Ward, Jr. and McCulloch (1947), Goldman-Rakic, Bates, and Chafee (1992), Barbas (2000a) and Luebke, Barbas, and Peters (2010)]. As discussed below, the key thalamic nuclei of these prefrontal and premotor cortices are robustly linked with the basal ganglia, and several sites within the same nuclei receive the output of the cerebellum.

3. Thalamic nuclei associated with language

The role of the thalamus in language began to be appreciated with the introduction of stereotactic surgery, conducted in an attempt to ameliorate tremor and other motor symptoms in disorders such as Parkinson's disease. Patients with surgical lesions in the motor-related ventral lateral nucleus (VL; see Table 1 for nomenclature), showed deficits in naming objects and short-term verbal memory [reviewed in Petrovici (1980)]. The role of VL in language function was subsequently corroborated using the independent approach of electrical stimulation [reviewed in Johnson and Ojemann (2000)]. More recently, neuroimaging studies of aphasic patients with subcortical lesions have described deficits in language after damage to thalamic nuclei, including anomia, verbal paraphasias, reduced verbal output and fluency, with relative sparing of language comprehension (Nadeau & Crosson, 1997; Radanovic & Scaff, 2003). Similar deficits have been described after vascular lesions of the thalamus affecting the tuberothalamic and paramedian arteries, which supply the thalamic reticular nucleus (TRN) and several anterior, medial and ventral thalamic nuclei [reviewed in Schmahmann (2003)].

The thalamic infarcts that most frequently produce aphasia involve the left side, consistent with the lateralization of language to the left hemisphere in the majority of individuals, and the predominant ipsilateral connections between the thalamus and cortex. Because vascular or other lesions in humans usually affect more than one nucleus, it is not possible to attribute specific deficits to distinct thalamic nuclei. The difficulties in pinpointing the specific damage after vascular lesions are compounded in cases where blood flow is significantly reduced in several brain areas without apparent damage to the system that is visible in images of the living brain [reviewed in Nadeau and Crosson (1997)]. In spite of these difficulties, the collective evidence from stereotactic surgery, electrical stimulation and imaging studies in aphasic patients with thalamic stroke implicate the VL, MD, intralaminar (especially the centromedian–parafascicular, CnMd–Pf) and the VA nuclei as the most likely candidates with a significant role in language [(Carrera & Bogousslavsky, 2006; Carrera, Michel, & Bogousslavsky, 2004; Nadeau & Crosson, 1997); reviewed in Schmahmann (2003)].

The above thalamic nuclei have several features in common: they receive the output of the basal ganglia and/or the cerebellum, two structures that have key roles in language processes. These nuclei are also connected with the frontal cortex, which includes the frontal language areas, other lateral and medial premotor areas as well as dorsolateral prefrontal areas implicated in cognitive tasks and sequential processing, which have an integral role in language processing, as elaborated below.