New Insight in The Neurophysiology of Broca Area

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The investigation of localization of the brain areas involved in speech production (motor component of speech) began in the middle of 19 th century by the work of Paul Broca (1824-1880). He was the first who clinically and anatomically investigated two patients who lost the ability to speak (motor aphasia). Both patients had lesion in the inferior frontal gyrus, therefore Broca concluded that this regions have a essential role in speech production.

From the time of Broca's discovery, one of the methodology which has been showing much progress in the field of speech production mechanism, is the use of electrical stimulation of the brain intraoperatively. These method requires the patient to be awake during craniotomy. The intraoperative electrical stimulation is routinely used for monitoring and mapping functional integrity of different brain regions (motor cortex, expressive and receptive speech areas). A standard neurophysiologic method is to locate by electrical stimulation the presumable eloquent cortex that produces speech arrest during various speech tasks. Since than many studies investigated speech production, using different methodologies (e.g. CT, fMRI, PET, MEG, EEG, TMS). Besides the great achievement of those methods, intraoperative electrical stimulation still remains patients standard of care and goal standard in the surgery of eloquent cortices.

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In order to test patients for motor, sensory, and/or language and speech region, neurosurgeon moves the sterile stimulating electrodes from one brain region to the next. Electrical stimulation to a small region of cortical surface results in a movement of face or limbs or speech arrest (the patients stops talking). If the stimulated cortical areas produces a previously described responses, than the brain region is considered important for that particular function (Schrader, 2008).

Results of electrical cortical electrical stimulation in awake patients during local anaesthesia or patients with subdurally implanted electrodes, has shown:

- Stimulation of somatomotor regions results in contraction of limbs, oro-facial muscles and vocalization (Penfield & Rasmussen, 1957; Penfield & Roberts, 1959)
- Stimulation of subcortical pathways (arcuate fasciculus, inferior frontooccipital fasciculus, subcallosal fasciculus, frontoparietal phonological loop) results in temporary speech and language disturbances (Duffau et al., 2008)
- Functional connections between specific brain regions participating in speech production (between Broca's area and primary motor cortex (M1) for laryngeal muscles and from M1 and laryngeal muscles) (Greenlee et al., 2004; Deletis et al. 2008; Deletis et al., 2009, Deletis et al., 2014, Rogic et al. 2014)
- Stimulation of Broca's region, primary motor cortex and negative motor areas result in speech arrest (Penfield & Rasmussen, 1957; Ojemann & Mateer 1979; Lesser et al., 1984; Lüders et al., 1995; Quiñones- Hinojosa et al., 2003;Bello et al., 2007, Sanai et al., 2008, Keles et al., 2004).

Detection of speech production areas

Almost all studies using electrical stimulation in awake patients and when inducing speech arrest, concluded that those regions have impact in speech production. Prerequisites for these studies that during surgery the patient has to be awake and actively participate in different speech tasks.

One of the goals when operating within the brain eloquent areas is to preserve their function by avoiding speech and language deficits. The recent longitudinal study of Ilmberger (2008) was designed to evaluate language functions pre- and postoperatively in patients who underwent microsurgical treatment of tumors in close proximity to or within language areas and to detect those patients at risk for postoperative aphasic disturbance. The results showed that the risk factors for postoperative aphasic disturbances were preoperative aphasia, intraoperative complications, language-positive sites within the tumor and non-frontal lesion location. The results of this study indicate that every attempt should be undertaken to preserve language and speech relevant areas intraoperatively, even when they are located within the tumor.

Surgical practice showed that injuries to certain speech areas (negative motor areas, supplementary motor area and primary motor area for laryngeal muscles) do not produce permanent deficit of speech production. However, it does not hold for lesions in the phonological part of the Broca area (Brodmann's area 44) which results in permanent aphasia.

Compared to these studies, we will investigate not only the clinical effect of electrical stimulation inducing speech arrest, but recording the neurophysiologic markers (different events recorded from laryngeal muscles) with and without speech production. Stimulating several brain regions

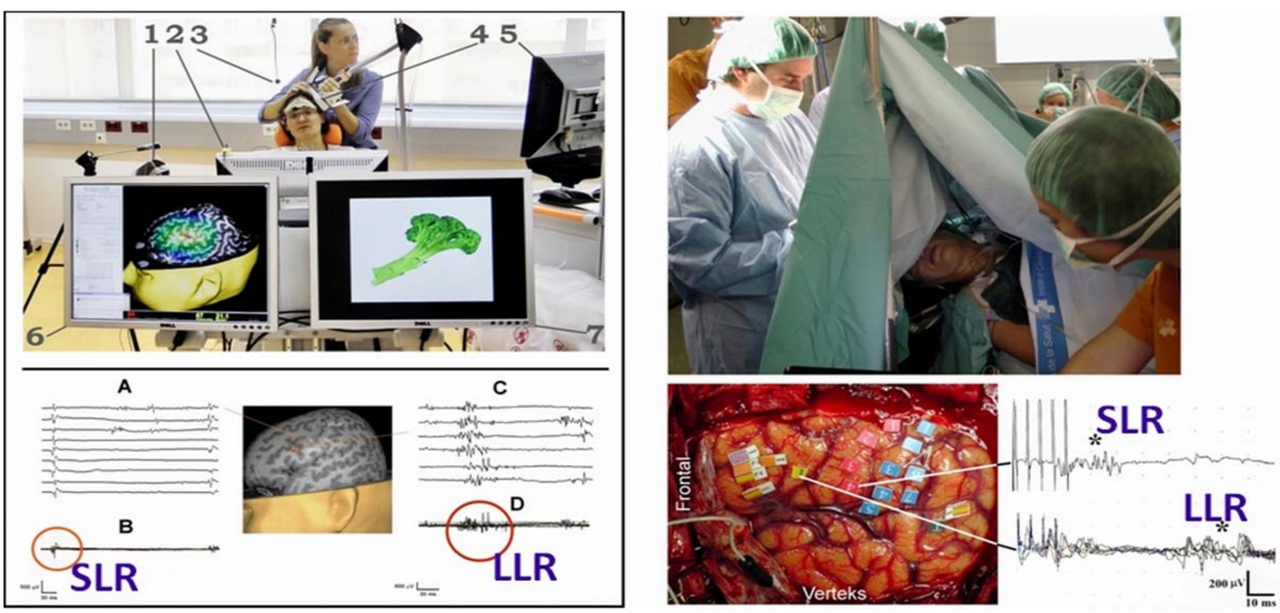

Figure 1. Left up: Subject during naming visually presented object and examiner holding the coil over on the dominant hemisphere with stimulation localized over the opercular part of Broca's area (Legend: 1=microphone connected to EMG amplifier, 2=monitor with visual object presented to the subject and the attached photo sensor, 3=microphone connected with the video camera, 4=magnetic coil for nTMS, 5= monitor with MRI for precise determination of stimulation site, 6=cloned monitor 5 for video shooting, and 7= cloned monitor 2 for video shooting). Left down: Neurophysiologic markers of M1 for laryngeal muscles (SLR) and of opercular part of Broca's area (LLR) for one subject Left: A) Repeatability of SLR and B) superimposed SLR; Right: C) Repeatability of LLR and D) superimposed LLR. In the Middle: 3D MRI with localisation of stimulated spots. Right: The results of intraoperative cortical mapping. Stimulation of the cortical spot marked in red (4) elicited SLR, while cortical spot marked in yellow (1) elicited LLR in cricothyroid muscle. From the same spot where LLR was elicited, speech arrest was induced for Spanish. (T=tumor location; Blue markers 1-7=somatosensory cortex; Red markers 1-4 primary motor cortex; Asterisks to the right depict SLR and LLR.

(Broca region, negative motor areas, primary motor region) and recording muscle responses in laryngeal muscles, we could specifically identify neural generators involved in speech production. For this purpose we will use a novel methodological approach (see: section methodology).

Our data (Deletis et al., 2008; Deletis et al., 2009), using a novel neurophysiologic methodology, indicates that stimulation of the motor speech areas by electrical or magnetic stimuli generate distinctive and time-locked responses in the intrinsic laryngeal muscles: short latency response (SLR), after stimulation M1 for laryngeal muscles, and long latency response (LLR), after stimulation of opercular part of Broca area. This approach allows us to intraoperatively find neurophysiologic markers of the speech motor eloquent cortices (Fig. 1).

Besides intraoperative electrical stimulation or stimulation through the implanted grid electrodes, neurophysiologic markers can be detected as well as speech arrest could be achieved by using pattern of short bursts of stimuli i combination with time locked visual object naming. The use of magnetic stimulation gives us unique opportunity to perform all studies on healthy subjects when combined with a MRI three-dimensional stereotactic guided neuronavigation system. This three dimensional system locate exact site of magnetic stimulation within brain surfaces. Its uses the identical principle as neurosurgical intraoperative navigation system to locate different brain regions after the brain has been exposed.

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