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Neurophysiologic markers in laryngeal muscles indicate functional anatomy of laryngeal primary motor cortex and premotor cortex in the caudal opercular part of inferior frontal gyrus

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HIGHLIGHTS

- This is a unique study describing methods for eliciting neurophysiologic markers of primary motor cortex (M1) for laryngeal muscles and premotor cortex of inferior frontal gyrus.
- The neurophysiologic markers were elicited by: (a) navigated transcranial magnetic stimulation (nTMS) in a group of healthy subjects, (b) direct cortical stimulation (DCS) of exposed cortex during craniotomy.
- These neurophysiologic markers indicate functional anatomy of M1 for laryngeal muscles and premotor cortex in the caudal opercular part of inferior frontal gyrus.

ABSTRACT

Objective: The aim of this study was to identify neurophysiologic markers generated by primary motor and premotor cortex for laryngeal muscles, recorded from laryngeal muscle.
Methods: Ten right-handed healthy subjects underwent navigated transcranial magnetic stimulation (nTMS) and 18 patients underwent direct cortical stimulation (DCS) over the left hemisphere, while recording neurophysiologic markers, short latency response (SLR) and long latency response (LLR) from cricothyroid muscle. Both healthy subjects and patients were engaged in the visual object-naming task. In healthy subjects, the stimulation was time-locked at 10–300 ms after picture presentation while in the patients it was at zero time.
Results: The latency of SLR in healthy subjects was 12.66 ± 1.09 ms and in patients 12.67 ± 1.23 ms. The latency of LLR in healthy subjects was 58.5 ± 5.9 ms, while in patients 54.25 ± 3.69 ms. SLR elicited by the stimulation of M1 for laryngeal muscles corresponded to induced dysarthria, while LLR elicited by stimulation of the premotor cortex in the caudal opercular part of inferior frontal gyrus, recorded from laryngeal muscle, corresponded to speech arrest in patients and speech arrest and/or language disturbances in healthy subjects.
Conclusion: In both groups, SLR indicated location of M1 for laryngeal muscles, and LLR location of premotor cortex in the caudal opercular part of inferior frontal gyrus, recorded from laryngeal muscle, while stimulation of these areas in the dominant hemisphere induced transient speech disruptions.
Significance: Described methodology can be used in preoperative mapping, and it is expected to facilitate surgical planning and intraoperative mapping, preserving these areas from injuries.

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1. Introduction

Mapping of primary motor cortex and Broca's area during awake craniotomy is not always the best option, especially in children and uncooperative patients; it would be important to find a neurophysiologic methodology for intraoperative mapping and monitoring anatomic and functional integrity of these cortical areas. The development of a methodology for preoperative identification using navigated transcranial magnetic stimulation (nTMS) would facilitate surgical planning and intraoperative mapping.

The primary motor cortex (M1) for laryngeal muscles has a role in execution and motor speech control, while the posterior inferior frontal gyrus, namely Broca's area, is regarded as an important motor speech cortical area having a role in all stages of word encoding and their unification (Sahin et al., 2009), as well as sending coded "commands" to M1.

After electrical stimulation of Broca's area, postsynaptic potentials of high amplitudes are recorded in the lateral part of the M1 (Greenlee et al., 2004). These results indirectly indicate a functional connection of Broca's area and M1 for face, mouth, pharynx, and larynx. It has been proposed that the critical parts of M1 needed to control vocalization are closely and uniquely associated with the laryngeal muscles (Corballis, 2003). The direct functional connectivity of M1 for laryngeal muscles was demonstrated in our studies (Deletis et al., 2008, 2009, 2011; Espadaler et al. 2012). In these studies, we have developed methodologies for stimulating M1 for laryngeal muscles and recording corticobulbar motor-evoked potentials (MEPs) from vocal and cricothyroid muscles. Corticobulbar MEPs can be regarded as a synonym for *short latency response* (*SLR*) representing a neurophysiologic marker of M1 for laryngeal muscles. It has been also reported that *long latency response* (*LLR*) can be recorded from laryngeal muscles after magnetic stimulation of the frontal cortex (Amassian et al., 1988; Ertekin et al., 2001). We also recorded LLRs intraoperatively but we neither studied this systematically nor investigated or speculated about its exact origin (Amassian et al., 1988; Ertekin et al., 2001; Deletis et al., 2008, 2011).

The standard intraoperative neurophysiologic method for mapping of Broca's area and M1 for orofacial, pharyngeal, and laryngeal muscles consists of electrical stimulation of these areas and inducing transient speech disruptions: (a) speech arrest and/or language disturbances while stimulating Broca's area and (b) dysarthria while stimulating M1 for orofacial, pharyngeal, and laryngeal muscles. Electrical stimulation with 50–60 Hz is used during surgery or through the subdural grid electrodes. In addition to 50-Hz stimulation for 1–3 s, speech arrest was also elicited with a short train of stimuli technique (5 pulses, 3-ms interstimulus interval) (Axelson et al., 2009). Furthermore, high-frequency repetitive transcranial magnetic stimulation with a repetition rate of 2–25 Hz was also used, but so far, only three groups of authors reported induced speech arrest (Epstein et al., 1996, 1999; Pascual-Leone et al., 1991). Recently, Picht et al. (2013) showed a good overall correlation between repetitive navigated (nTMS) and direct cortical stimulation (DCS) during awake surgery for the identification of language-related areas in patients with left-hemisphere lesions.

We hypothesized that time-locked electrical activity is recorded in laryngeal muscles after the stimulation of M1 for laryngeal muscles and of premotor cortex in the caudal opercular part of inferior frontal gyrus.

Therefore, the goal of this study was to investigate the relationship between cortical spots generating neurophysiologic markers recorded in laryngeal muscle and the functional role of these cortical areas by clinically producing transient speech disruptions.

2. Methodology

2.1. Healthy subjects/patients

Ten right-handed healthy subjects, three male and seven female, average age 31 ± 13.32 (range 22–66 years), and 18 right-handed patients, 10 male and eight female, average age 46.2 ± 13.69, range 27–68 years, were included in the study. The Edinburgh Inventory Questionnaire test (Oldfield, 1971) was used for assessment of handedness. All healthy subjects and patients signed informed consent forms to participate in the study. Healthy subjects received a small honorarium. The study was approved by the Ethical Committees of School of Medicine, University of Split, Croatia, and University Hospital Bellvitge, Barcelona, Spain.

2.2. Healthy subjects group

2.2.1. Magnetic resonance imaging (MRI) and navigated transcranial magnetic stimulation (nTMS)

Magnetic resonance imaging (MRI) of the head for each subject was performed with Siemens Magnetom Avanto, Tim (76 × 18) strength 1.5 T. MRI images were recorded by specific MRI requirements for nTMS-NBS (Navigated Brain Stimulation), Nexstim System 4 (Helsinki, Finland), including the head, visible ears, and nose. MRI images are integrated in the nTMS machine with a three-dimensional navigation system display of the subjects' brain. Sophisticated real-time data processing allows the precise display of the induced electric field (E-field) within the brain tissue. Targeting tools available on-screen are the following: grid for systematic brain mapping, targeting tool for optimal coil placement, aiming tool for precise repetition of given stimuli, and automated stimulation (location controlled). The subject wears an optical head tracker and by using a pointer, 12 points are registered on the subject's scalp. An air-cooled eight-shaped figure coil was used, generating a biphasic pulse of 289 μs pulse length. The maximum E-field is 172 V/m below the Nexstim Focal coil in the spherical conductor model representing the human head.

The nTMS mapping procedure is as follows:

1. Eliciting MEP resting threshold for hand muscle, abductor pollicis brevis (APB);
2. Mapping of the very lateral part of M1 and recording SLR in cricothyroid muscle during the visual object-naming task;
3. Mapping of the inferior frontal gyrus and recording LLR in cricothyroid muscle during the visual object-naming task;
4. Stimulation of cortical spot which elicited SLR to produce transient speech disruption during the visual object-naming task;
5. Stimulation of cortical spot which elicited LLR to produce transient speech disruptions during the visual object-naming task.

Mapping of the M1 for hand muscle is the standard method in nTMS studies dealing with mapping of M1 (Epstein et al., 1999; Schmidt et al., 2009; Julkunen et al., 2011) and its vicinity (Jennum et al., 1994; Michelucci et al., 1994; Epstein et al., 1999; Stewart et al., 2001), and as a standard intraoperative procedure preceding mapping of primary motor cortex and Broca's area (Duffau, 2008; Kim et al., 2009; Lubrano et al., 2010). Mapping over the left M1 for APB was determined by the "omega knob" on axial MRI images, or a "hook structure" at the sagittal MRI (Yousry et al., 1997). The central sulcus was also used as a landmark while moving the coil in the anterior–posterior direction in order to map the hot spot for M1 for APB. The MEP resting threshold was defined as the lowest stimulus intensity for eliciting at least five MEPs in the APB muscle