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Neuroscience Letters 352 (2003) 85–88

Neuroscience Letters

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Cortical excitability changes associated with musical tasks: a transcranial magnetic stimulation study in humans

Y.L. Lo[a,*], S. Fook-Chong[b], D.P.C. Lau[c], E.K. Tan[d]

[a]Department of Neurology, National Neuroscience Institute, Singapore General Hospital, Outram Road, Singapore 160608, Singapore
[b]Department of Clinical Research, Singapore General Hospital, Outram Road, Singapore 160608, Singapore
[c]Department of Otolaryngology, Singapore General Hospital, Outram Road, Singapore 160608, Singapore
[d]Department of Neurology, Singapore General Hospital, Outram Road, Singapore 160608, Singapore

Received 26 July 2003; received in revised form 12 August 2003; accepted 14 August 2003

Abstract

Neuroimaging studies have suggested differences in cortical activation in human vocalization and musical tasks. However, functional neurophysiological evidence on cortical excitability changes is lacking. We utilized transcranial magnetic stimulation to demonstrate changes in cortical excitability during overt humming and singing tasks. The findings complement those from neuroimaging and support the existence of separate bilateral deep-seated neural networks, as distinct from those for vocalization.

Keywords: Cortical excitability; Musical tasks; Vocalization; Transcranial magnetic stimulation

The left hemisphere is dominant for speech and language functions in the majority of right-handed individuals [6,20]. A previous transcranial magnetic stimulation (TMS) study [18] demonstrated increased excitability in the dominant motor cortex consistently during reading but not during spontaneous speech. Singing, another form of communication, possesses additional aspects of rhythm, pitch variation, auditory feedback mechanisms and possibly, emotional content.

Hemispheric lateralization in humans during singing is less certain. Previous studies have suggested both right [8, 21] and left sided [1] involvement. In this first study using TMS, we investigate motor cortex excitability during the overt execution of musical tasks. Its findings are discussed in comparison with existing knowledge on human vocalization.

We studied nine right-handed, musically-naive subjects (four males) aged 23–41 with informed consent. The study protocol was approved by the institutional ethics committee. Subjects were selected from a pool of normal volunteers for their ability to hum and sing tunes with good musical prosody. TMS was performed with a Magstim eight-shaped coil (Magstim, Whitland, UK) 70 mm in diameter capable of generating a peak magnetic field of 2.2 Tesla, in conjunction with a Magstim 200 unit. For upper limb recording in the first dorsal interossei (belly-tendon configuration), optimal position of stimulation, with a forward anteromedial induced current, lies approximately 5 cm lateral and 1 cm anterior to the vertex. Motor evoked potentials (MEP) were elicited with stimulation intensity at 10% above the relaxed threshold, defined as the lowest TMS intensity to elicit MEPs of 100 μV peak to peak amplitude in five of ten successive stimulations in a relaxed muscle. Continuous electromyography with audio feedback ensured that MEPs were recorded in the fully relaxed state. Hence, MEP responses deemed facilitated were discarded. For lower limb recordings in the abductor hallucis muscle, a Magstim 90 mm circular coil elicited reproducible MEPs, usually at 70–80% stimulator output intensity. To ensure optimal coil position for lower limb MEP recording, simultaneous upper limb MEP recordings were made. The position which produced the largest lower limb MEPs without generating upper limb MEPs was usually 2–3 cm anterior to the vertex [17]. In our experience, this coil produced more reproducible and unilaterally activated lower limb MEPs than the double cone coil. To further ensure correct stimulation, only MEPs of similar mor-

* Corresponding author. Tel.: +65-6-326-5003; fax: +65-6-220-3321.
E-mail address: gnrlyl@sgh.com.sg (Y.L. Lo).

0304-3940/03/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/S0304-3940(03)01016-4

phology were accepted. Ten MEPs were obtained before and during each task, with each experimental block performed in a randomized order. The first TMS pulse was delivered 5 s after the onset of singing or humming. Each TMS pulse was delivered at adequate intervals of 5–6 s. For control studies, subjects were advised to keep relaxed but alert. For the musical tasks, humming and singing continuously of a familiar 'Happy Birthday' song at constant tempo and volume were utilized. Additionally, the subjects performed a reading task, consisting of reciting aloud a textbook passage in the English language. The subject of the passage were technical and deliberately chosen for its absence of emotional content. Using a similar protocol as musical tasks, ten TMS pulses were delivered before and during reading tasks bilaterally to obtain MEPs. To minimize the number of TMS shocks delivered per subject, we studied MEPs recorded from the abductor hallucis only, as upper limb MEP changes during reading were previously studied [18].

All studies were carried out with subjects seated comfortably in a quiet environment. MEPs were amplified and filtered with a Dantec Counterpoint machine (Dantec, Skovlunde, Denmark) with a band pass of 20–2000 Hz. Peak to peak MEP amplitudes (in mV), after natural logarithmic transformation, were compared statistically with analysis of variance (ANOVA) using SPSS for Windows Version 10.1.

Mean TMS thresholds for upper limb (left cortex: 59%, right: 56%) and lower limb (left cortex: 71%, right: 75%) MEP studies were not significant with side comparison (Student's t-test, $P > 0.05$).

Three-factor ANOVA was performed using task, time and side as factors. Each factor had two levels respectively: hum and sing; before and during task; right and left sides. For upper limbs, time ($F = 23.01$, $P < 0.001$) and side ($F = 7.35$, $P = 0.007$) were significant. For lower limbs, only time was significant ($F = 15.3$, $P < 0.001$). No interaction was found between all three factors. We performed further subgroup analysis using one factor ANOVA for each upper and lower limb and side, using time as a factor. This showed that with the exception of right upper limb (left cortex stimulation) during humming ($P = 0.06$), all seven other subgroups were significant ($P < 0.05$), indicating increased cortical excitability as a result of performing each musical task.

'H' reflex studies with flexor carpi radialis (upper limb) and soleus (lower limb) recordings were performed with a similar protocol. All three factors, task ($F = 0.72$, $P = 0.54$), time ($F = 0.51$, $P = 0.45$) and side ($F = 0.55$, $P = 0.49$) were not significant, suggesting a supraspinal origin for increased excitability. To validate our results, five subjects consented to a repeat experiment of musical tasks. Subjects both hummed and sung the tune 'Twinkle Twinkle Little Star' with TMS applied using an identical protocol. This repeat study yielded similar results to the initial experiment.

For reading tasks, a two-factor ANOVA, with time and side as factors, showed time to be significant ($F = 14.72$, $P < 0.001$). Further analysis using one factor ANOVA with time as a factor showed significant MEP amplitude facilitation only with left TMS ($P < 0.01$).

Experimental results are summarized in Figs. 1 and 2. Fig. 3 shows actual MEP recordings for one subject during musical tasks.

TMS is a well-recognized technique for the study of corticospinal function [9]. Surface TMS can produce direct activation of corticospinal neurons to lower limb muscles [14] and has been shown to activate the leg motor area using functional magnetic resonance imaging (fMRI) [17]. Due to intrinsic variations in cortical excitability, we averaged multiple MEP amplitudes during each task to obtain more accurate values. Additionally, we repeated the study under the same experimental conditions to ensure validity. All subjects studied were able to perform musical tasks fluently with no difficulty.

Our ANOVA results showing higher right upper limb MEP amplitude from left cortex TMS may be related to right-handedness of all subjects, which were stimulated at a constant intensity above resting threshold before and during all tasks [19].

Direct electrical stimulation over the left inferior frontal cortex [12] and repetitive transcranial magnetic stimulation (rTMS) of the left precentral gyrus have produced speech arrest [4]. The likely underlying mechanism involves disruption of language function of Broca's area or motor cortex function at the area of facial muscle representation respectively. Our findings of significant MEP facilitation with left cortex TMS corroborated those of Tokimura et al. [18], as well as fMRI studies showing activation in the left middle temporal gyrus, midfrontal gyrus and inferior frontal gyrus [7]. Furthermore, it demonstrates the occurrence of more widespread increase in left motor cortex excitability in the leg area, spatially distanced from the hand and face areas, rather than attributing previous findings to overflow activation from the mouth representations [18]. Indeed, the cingulate and paracingulate areas close to the leg representation, has been shown to be engaged in word generation tasks with fMRI studies [2].

While vocalization was seen to be of left dominance, the

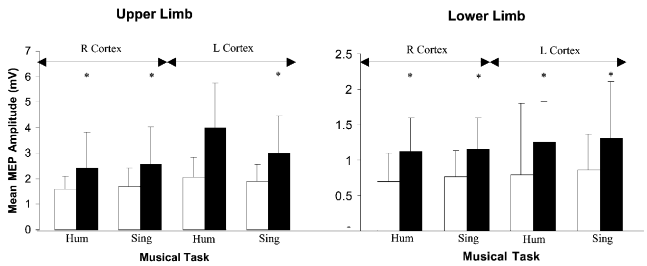

Fig. 1. Mean MEP responses from right and left cortex stimulation before (un-shaded) and during (shaded) musical tasks in upper and lower limb recordings. Error bars represent one standard deviation from the mean. *$P < 0.05$.

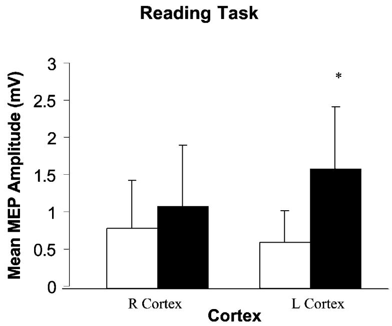

Fig. 2. Mean MEP responses from the right and left cortex stimulation before (unshaded) and during (shaded) reading tasks in lower limb recordings. Error bars represent one standard deviation from the mean. *$P < 0.01$.

musical tasks had largely right-sided or bilateral effects, as seen from our findings. Humming produced increased excitability more in the right than left motor cortices, with no significant increased excitability in the left cortical region with right upper limb recordings. Singing, with words and melody, resulted in bilateral increased excitability in both upper and lower limb recordings, indicating increased motor cortex excitability bilaterally. A possible region close to the leg area involved could be the cingulate cortex. Direct electrical stimulation of this area has been shown to produce motor responses in the contralateral leg [3]. Cingulate and paracingulate area activation, as noted previously, has been demonstrated during vocalization and word generation tasks with functional neuroimaging [2,5].

Humming, the production of melody without word articulation, corroborated findings of a fMRI study which showed that production of a non-lyrical tune elicited activation predominantly in the right motor cortex [15]. During actual singing tasks, however, significant excitability changes observed bilaterally were consistent with cerebral blood flow changes measured with PET in the supplementary motor areas, anterior cingulate cortex and

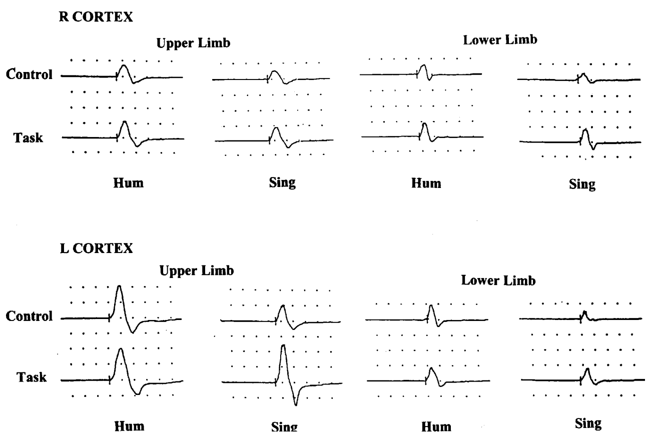

Fig. 3. Actual MEPs of one subject from right and left cortex stimulation. The top trace (control) was obtained before and the bottom trace (task) after each task. Vertical gain was 1 mV/division. Horizontal sweep speeds were 5 ms/division and 8 ms/division for upper and lower limb recordings, respectively.

precentral gyri [13]. Our TMS findings thus corroborated these results obtained from functional imaging.

Our findings further corroborated results of rTMS studies. The failure of song arrest, as opposed to speech arrest, using rTMS over different regions in the left or right frontal lobe, argues for the existence of separate neural networks subserving vocalization and singing [16]. Significant changes in cortical excitability from lower limb recording support the participation of a diffuse, deep-seated cortical circuitry during singing tasks resistant to the unilateral surface disruption effects of rTMS.

In conclusion, we provide new functional neurophysiological evidence showing changes in cortical excitability melody generating tasks. These findings, using TMS for the first time, may be of relevance in the clinical setting. With the advent of music therapy for various neurological diseases [10], the evidence suggesting more robust and distinct neural pathways for singing tasks supports its early utilization for rehabilitative purposes. These aspects can be further explored in future clinical studies.

Finally, our study differs from previous imaging studies, which utilized single pitch repetition [13] or recitation of a non-lyrical tune [15] rather than a dynamic task of overt singing aloud. Given the difficulties encountered in fMRI studies of overt speaking from motion artifacts [11], TMS can play a contributory role in understanding the cortical mechanisms in musical tasks acquired through functional imaging.

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