Task-dependent modulation of functional connectivity between hand motor cortices and neuronal networks underlying language and music: a transcranial magnetic stimulation study in humans


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Abstract

Although language functions are, in general, attributed to the left hemisphere, it is still a matter of debate to what extent the cognitive functions underlying the processing of music are lateralized in the human brain. To investigate hemispheric specialization we evaluated the effect of different overt musical and linguistic tasks on the excitability of both left and right hand motor cortices using transcranial magnetic stimulation (TMS). Task-dependent changes of the size of the TMS-elicited motor evoked potentials were recorded in 12 right-handed, musically naive subjects during and after overt speech, singing and humming, i.e. the production of melody without word articulation. The articulation of meaningless syllables served as control condition. We found reciprocal lateralized effects of overt speech and musical tasks on motor cortex excitability. During overt speech, the corticospinal projection of the left (i.e. dominant) hemisphere to the right hand was facilitated. In contrast, excitability of the right motor cortex increased during both overt singing and humming, whereas no effect was observed on the left hemisphere. Although the traditional concept of hemispheric lateralization of music has been challenged by recent neuroimaging studies, our findings demonstrate that right-hemisphere preponderance of music is nevertheless present. We discuss our results in terms of the recent concepts on evolution of language and gesture, which hypothesize that cerebral networks mediating hand movement and those subserving language processing are functionally linked. TMS may constitute a useful tool to further investigate the relationship between cortical representations of motor functions, music and language using comparative approaches.

Introduction

‘Men sang out their feelings long before they were able to speak their thoughts’ (Jespersen, 1922). Singing, the act of producing musical sounds with the voice, is so basic to humans that its origins are unknown and may even predate the development of spoken language. There has been a long-standing debate among neuroscientists about how the brain processes music and language. Traditionally, it has been believed that both entities represent distinct systems, which are handled independently in each hemisphere. This classical view of reciprocal cerebral hemispheric dominance has been challenged by modern neuroimaging studies, which suggest that music and language share certain brain resources (e.g. Perry et al., 1999; Riecker et al., 2000; Jeffries et al., 2003; Patel, 2003; Brown et al., 2004, 2006).

Transcranial magnetic stimulation (TMS) provides a complementary tool to investigate hemispheric lateralization of language- and music-related cortical networks. In the majority of studies, TMS is applied to disturb a particular cortical area, which in turn demonstrates that this area is essential for performance of the task studied (Pascual-Leone et al., 2000). In this context, a striking finding has been the arrest of speech output during rapid stimulation over the left inferior frontal region (Pascual-Leone et al., 1991; Epstein et al., 1999; Aziz-Zadeh et al., 2005). However, another possible approach to assess hemispheric lateralization by TMS is to evaluate the effect of cognitive functions on motor cortex excitability as expressed in changes of the size of the TMS-induced motor evoked potentials (MEPs) (e.g. Papathanasiou et al., 2004; Theoret et al., 2004; Molnar-Szakacs et al., 2005). In general, it is thought that such interactions between functional systems underlying the task performed and the motor cortex are of nonspecific (i.e. indirect) origin. However, the observations that production (e.g. Tokimura et al., 1996; Seyal et al., 1999; Meister et al., 2003, 2006) as well as reception (e.g. Floel et al., 2003) of language predominantly increase the cortical excitability of the hand representation in the language-dominant (i.e. left) hemisphere may suggest a closer relationship between the cortical networks mediating language processing, planning and execution of hand movements.

In the present study, we examined if, and to what extent, musical tasks modulate the excitability of left and right hand motor regions differentially. We used single-pulse TMS in a comparative approach to...
record MEPs from both hands during overt speech, singing and humming. The articulation of meaningless syllables served as control condition. We hypothesized that changes in the amplitude of hand MEPs depend on the site of stimulation and task, which in turn may reflect different degrees of hemispheric lateralization for music and language in the human brain.

Materials and methods

Subjects

Fourteen right-handed, musically naive, male subjects participated in this experiment after giving written, informed consent. The mean age was 26.5 years (range 21–34 years). Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). None of the subjects had a history of neurological disorders, including seizures. The study was performed in accordance with the Declaration of Helsinki (1964). The protocol was approved by the ethics committee of the Faculty of Medicine at the RWTH Aachen University.

Transcranial magnetic stimulation

Transcranial magnetic stimulation was applied with a Magstim 200 stimulator (Magstim Co., UK) using a figure-of-eight coil. The site of stimulation was adjusted in order to elicit MEPs with maximum amplitude in the contralateral first dorsal interosseus muscle (M1-Hand). MEPs were obtained with surface Ag/AgCl electrodes. The output of the magnetic stimulator was adjusted to about 120% of the motor threshold at rest. The resting motor threshold was defined as the lowest stimulation intensity that evoked five MEPs with peak-to-peak amplitude of > 50 µV in 10 trials in the relaxed first dorsal interosseus muscle. Background electromyography activity was continuously monitored in order to ensure that MEPs were recorded during full relaxation.

Stimuli and tasks

Motor cortex excitability was tested while the subjects performed one of four different tasks [singing aloud (SiA), humming (H), speaking aloud (SpA) or nonverbal oral movement (M)]. All experimental material was in German. For the musical tasks (i.e. SiA and H) subjects were presented with 12 songs (e.g. nursery rhymes or folksongs) and 12 melodies. The melodies were derived from famous classical pieces (e.g. W.A. Mozart’s ‘Eine kleine Nachtmusik’ Serenade for String Quartet and Bass K. 525). It was assumed that the selected tunes could not be associated with any particular lyric by the subject as the tunes have never been recorded with any lyrics. Subjects chose five songs for the singing task and five melodies for the humming task, respectively. Prior to the main experiment, subjects trained in singing and humming these songs and melodies until they felt sufficiently familiar with the words and/or melodies. Subjects were instructed to sing or hum a song continuously at constant tempo and volume. For the SpA condition, subjects chose five out of 10 popular sayings. The recitation of these five sayings was also practiced during the training session. For the M task subjects were required to articulate repetitively the three meaningless syllables ‘pa’, ‘ta’ and ‘ka’. As baseline condition, meaningless figures consisting of nonletter strings were presented. These had to be viewed passively.

In comparison to previous studies, we used a random experimental design instead of block-wise testing (Lo et al., 2003; Lo & Fook-Chong, 2004). All conditions (SiA, H, SpA, M and baseline) were tested in one trial, with 10 items each. In a previous study, speech-related modulations of motor cortical outputs were found to be less prominent in subjects with extensive musical training, which suggests that task complexity could play an important role (Lin et al., 2002). In our study subjects were therefore required to continuously switch modality (i.e. SiA, H, SpA and M) and content (i.e. song, melody, saying or syllables), respectively. The order of items was pseudo-randomized. Both hemispheres were examined in separate sessions. The order of sessions was counterbalanced across subjects.

All studies were carried out with subjects seated comfortably in a reclining chair. They were instructed to focus their attention on a computer screen (21 in, 75 Hz, viewing distance 60 cm). In the main experiment each condition was signaled by a visual cue presented on the screen using PRESENTATION software (Version 0.51, Neurobehavorial Systems, Albany, CA, USA). We chose easy associative drawings as cues for SiA, H and SpA instead of written or spoken instructions in order to avoid any interference from phonological or semantic processes related to word identification. Black dots were used as cues for the M task. In each condition one TMS pulse was administered 4–8 s after the voice onset, which was measured by means of a microphone attached to the subject’s collar. The time interval was randomly varied in order to avoid anticipation of stimulation. Subjects were instructed to execute each task trial until a TMS pulse was given (i.e. over a period of 4–8 s). There was a time interval of 10 s between the tasks during which a fixation cross was shown.

Control experiment

We conducted a control experiment to exclude an effect of task sequence (i.e. that the previous task may have influenced the following task due to long-lasting MEP changes). Ten subjects consented to repeat the experiment. In this session, the TMS pulse was administered 2–4 s after the subject stopped speaking, singing or humming, respectively. As subjects were required to execute each single task for the same amount of time, a stop signal was presented on the screen after 6 s. MEPs were collected in the same manner as described above.

Analysis

Peak-to-peak amplitude measurements of all MEPs were recorded. MEPs contaminated by voluntary muscle activity (i.e. increase in EMG activity before the stimulation artifact) were discarded (approximately 3% of the recordings). Mean MEP amplitudes obtained during experimental conditions were normalized to the mean MEP obtained during viewing nonletter strings (baseline condition). Thus, relative amplitudes were calculated that indicated the change in cortical excitability in response to task compared with baseline. This computation allowed a direct comparison among different trials and subjects. For statistical evaluation the relative amplitudes were analysed with a two-factor repeated measures ANOVA with task (four levels: SiA, H, SpA and M) and site (two levels: left vs. right motor cortex) as within-subject factors. We made posthoc comparisons between single factors using Duncan’s test (α = 0.05).

Results

None of the subjects experienced any adverse effects of TMS. The mean motor threshold of both hemispheres did not differ significantly \[ P = 0.23; \text{left motor cortex, 37.7 ± 10.8% (SD); right motor cortex, 43.1 ± 12.3% of maximum stimulator output}. \] The amplitudes of the baseline conditions of the two hemispheres were compared with the
Mann–Whitney U-test and revealed no significant differences. Thus, as expected, passive viewing of nonletter strings could be used as a baseline condition. The average MEP amplitudes for the baseline condition ranged between 0.58 and 0.69 mV.

All other conditions showed significant increases by factors ranging between 1.2 and 1.9 in comparison to this baseline ($P < 0.03$) (Fig. 1). The analysis of mean relative amplitudes of the experimental tasks by means of ANOVA revealed a significant interaction between site and task ($F_{1,13} = 5.07, P < 0.04$). These differential effects were further explored by means of posthoc analysis of single contrasts for each condition. Stimulation of the left motor cortex during SpA led to a significant facilitation in comparison with M ($P < 0.03$). Motor cortex excitability was therefore significantly increased in the language dominant hemisphere while subjects were speaking aloud. In contrast to the results obtained from left hemisphere stimulation, MEP amplitudes following right hemisphere stimulation remained unchanged during SpA. Moreover, mean MEP amplitudes were significantly increased for the SiA and H tasks compared with M following right motor cortex stimulation ($P < 0.02$). Taken together, these results indicate an increase in the excitability of the hand area of right motor cortex but not the left hand motor region during musical tasks (e.g. SiA and H).

The analysis of the control experiment showed that MEP amplitudes were not significantly different from baseline for all conditions (SiA, H, SpA and M) ($P > 0.2$) (Fig. 2). Hence, these results indicate that motor cortex excitability returned to baseline 2–4 s after the end of task execution. An influence of the previous task on the following seems thus to be unlikely.

**Discussion**

The main findings of our study were reciprocal lateralized effects of overt speech and musical tasks on hand motor cortices in right-handed subjects. The corticospinal projection of the left (i.e. dominant) hemisphere to the right hand during overt speech was facilitated. There was no effect on the right hemisphere during or after speaking. Moreover, we show that excitability of the nondominant (i.e. right) motor cortex increases during both overt singing and humming, whereas no effect could be found on the left hemisphere.

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**Fig. 1.** Mean motor evoked potential (MEP) responses from left and right cortex stimulation during experimental tasks: singing aloud (SiA), humming (H), speaking aloud (SpA) or nonverbal oral movement (M). Opposite hemispheric changes of motor cortex excitability were found during language and musical tasks. Error bars indicate SEM. *$P < 0.05$. TMS, transcranial magnetic stimulation.

**Fig. 2.** Mean motor evoked potential (MEP) responses from left and right cortex stimulation after experimental tasks: singing aloud (SiA), humming (H), speaking aloud (SpA) or nonverbal oral movement (M). No significant changes were observed. Error bars indicate SEM. TMS, transcranial magnetic stimulation.

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The results differ from previous findings concerning right hemisphere involvement in musical tasks. Lo et al. (2003) observed that overt humming produced increased excitability more in the right than left motor cortices whereas overt singing resulted in bilateral increased excitability. Their investigation of the silent period as a measure of interhemispheric motor inhibition produced inconsistent results (Lo & Fook-Chong, 2004). During singing, transcortical inhibitory effects were found, originating from the right cortex. Surprisingly, no inhibitory changes, ipsilateral and contralateral, were evident with humming. Methodological differences in the experimental design may account for the disparity of results. For instance, we carefully selected melodies for the humming task that could not be associated with any particular lyric by the subject. In contrast, Lo et al. (2003; Lo & Fook-Chong, 2004) required their subjects to sing or hum continuously a particular lyric by the subject. Moreover, McChesney et al. (2003) observed that injection of sodium amylobarbitone into the right carotid artery produced deficient singing (Gordon & Bogen, 1974). Moreover, McChesney-Atkins et al. (2003) reported that an epileptogenic focus in the right inferior frontal region triggered seizures with singing as epileptic automatism (McChesney-Atkins et al., 2003). However, a major drawback of these case studies is that the underlying lesions have rarely been focal. Although there is indeed evidence for the view that music and language are localized predominantly to homologous regions of opposite hemispheres (for a review, see Peretz & Zatorre, 2005), the concept of a clear-cut hemispheric dissociation of music and language processing has been challenged by recent neuroimaging studies, which started to carefully distinguish parallels and differences between music and language (e.g. Patel, 2003; Brown et al., 2004; Koelsch et al., 2004; Peretz & Zatorre, 2005). On the basis of their PET data, Brown et al. (2006) have elaborated a comparative model with different levels of interaction. According to the model, some features of music and language involve identical or overlapping brain resources, whereas others are processed in parallel or distinctive ways.

Overall, it seems that language function is lateralized to a larger extent than music in the human brain. The neuronal networks underlying melodic production are probably more spread. However, our results demonstrate that right-hemisphere preponderance of music is nevertheless present. This notion is supported by growing evidence that prosody, i.e. the intonation of speech conveying emotional nonverbal connotation, is mainly processed in the right hemisphere (e.g. Hesling et al., 2005; van Rijn et al., 2005; Ethofer et al., 2006). The observation that singing was associated with less lateralization compared with humming, i.e. the production of melody without word articulation, could be the result of higher activation of left-sided shared neuronal components, which underlie both music and language processing.

Possible implications for the development of hemispheric specialization

In general, diverse cognitive tasks have been shown to modulate the excitability of corticospinal motor pathways in the absence of overt motor activity (e.g. Theoret et al., 2004; Molnar-Szakacs et al., 2005). Therefore, it is unknown at present whether the speech-related facilitation of the motor cortex excitability observed in our experiments reflects primarily a general hemispheric activation or the consequence of a specific relationship between the task-related brain regions and motor cortex. However, there is some evidence that the latter may apply for the functional connection between language and the hand movement system (Lin et al., 2002; Floel et al., 2003; Meister et al., 2003, 2006; Papathanasiou et al., 2004). In particular, the finding that the excitability of the hand but not leg area of the language-dominant hemisphere was enhanced suggests a specific intraindividual corticocortical link between language and the motor system (Meister et al., 2003; Sparing & Meister, 2006). This hypothesis is also supported by the investigations of hemispheric motor–language interactions in musicians (Lin et al., 2002). Furthermore, the concept of functional connectivity between hand motor cortex and language areas fits well with the theory of ‘gestural origin of language’ (Rizzolatti & Arbib, 1998; Corballis, 2003; Arbib, 2005).

From the evolutionary point of view, music may constitute a prototype communication system. In our study, utterances containing musical phrases predominantly enhanced the right hemisphere motor area. This suggests that the right hemispheric system for music processing has homolog functional connections with the hand motor system, probably as a result of the evolutionary specialization of the hemispheres. Darwin (1871) was among the first to state the hypothesis that song evolved before language or as a transitional state between subhuman primate vocalizations, prosody and speech. Although various researchers adopted this intriguing concept that music scaffolds the early structural aspects of a protolanguage (e.g. Jepsen, 1922; Richman, 1993; Mithen, 2006), experimental studies so far have found no clear evidence for it (for a review, see Fitch, 2006). Taken together, the underlying mechanisms of the functional connectivity found in the present study between the nondominant hand motor cortex and brain areas associated with music are not clear and further studies are needed.

Conclusion

Our study has shown reciprocal effects of musical and linguistic tasks on the excitability of the primary hand motor cortex. This finding supports the general concept of opposite hemispheric specialization for music and language in the human brain. In recent years, TMS has become a powerful tool to study the distributed effects of TMS on neural networks involved in a given behavior (Pascual-Leone et al., 2000). The assessment of task-dependent modulations of cortical excitability by means of TMS may be useful for future studies assessing the functional cortical networks underlying music and language, i.e. how the human brain processes music.
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Abbreviations

H, humming; M, nonverbal oral movement; MEP, motor evoked potential; SIA, singing aloud; SPA, speaking aloud; TMS, transcranial magnetic stimulation.

References