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Inhibitory Stimulation of the Ventral Premotor Cortex Temporarily Interferes with Musical Beat Rate Preference

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Abstract: Behavioral studies suggest that preference for a beat rate (tempo) in auditory sequences is tightly linked to the motor system. However, from a neuroscientific perspective the contribution of motor-related brain regions to tempo preference in the auditory domain remains unclear. A recent fMRI study (Kornysheva et al. [2010]: Hum Brain Mapp 31:48-64) revealed that the activity increase in the left ventral premotor cortex (PMv) is associated with the preference for a tempo of a musical rhythm. The activity increase correlated with how strongly the subjects preferred a tempo. Despite this evidence, it remains uncertain whether an interference with activity in the left PMv affects tempo preference strength. Consequently, we conducted an offline repetitive transcranial magnetic stimulation (rTMS) study, in which the cortical excitability in the left PMv was temporarily reduced. As hypothesized, 0.9 Hz rTMS over the left PMv temporarily affected individual tempo preference strength depending on the individual strength of tempo preference in the control session. Moreover, PMv stimulation temporarily interfered with the stability of individual tempo preference strength within and across sessions. These effects were specific to the preference for tempo in contrast to the preference for timbre, bound to the first half of the experiment following PMv stimulation and could not be explained by an impairment of tempo recognition. Our results corroborate preceding fMRI findings and suggest that activity in the left PMv is part of a network that affects the strength of beat rate preference. *Hum Brain Mapp 32:1300–1310, 2011.* © 2010 **Wiley-Liss, Inc.**

Key words: premotor cortex; rhythm; rTMS; auditory-motor integration

INTRODUCTION

A tight link exists between the motor system and preferred auditory rhythm [Todd et al., 1999]. The tempo range of different popular musical styles closely matches that of repetitive movements such as locomotion [Moelants, 2003; van Noorden and Moelants, 1999]. A series of behavioral studies demonstrated prior repetitive movement to prime preferences for musical rhythm in children and adults [Phillips-Silver and Trainor, 2005, 2007, 2008]. Likewise, a strong association has been shown between spontaneous motor tempo and preferred tempo of auditory stimuli which varies across age [McAuley et al., 2006] and between individuals [Todd et al., 2007]. Accordingly, beat rate (tempo), a periodic auditory pulse with an inter-onset-interval in a sub-seconds range peaking around 2 Hz [van Noorden and Moelants, 1999] corresponds to the preferred frequency of repetitive movements in adult individuals [McAuley et al., 2006]. A beat serves as a central auditory cue when synchronizing body movements to music [Drake et al., 2000; Fraisse, 1982; Kirschner and Tomasello, 2009; Styns et al., 2007] and appears to be a human universal [Nettl, 2000].

Additional Supporting Information may be found in the online version of this article.

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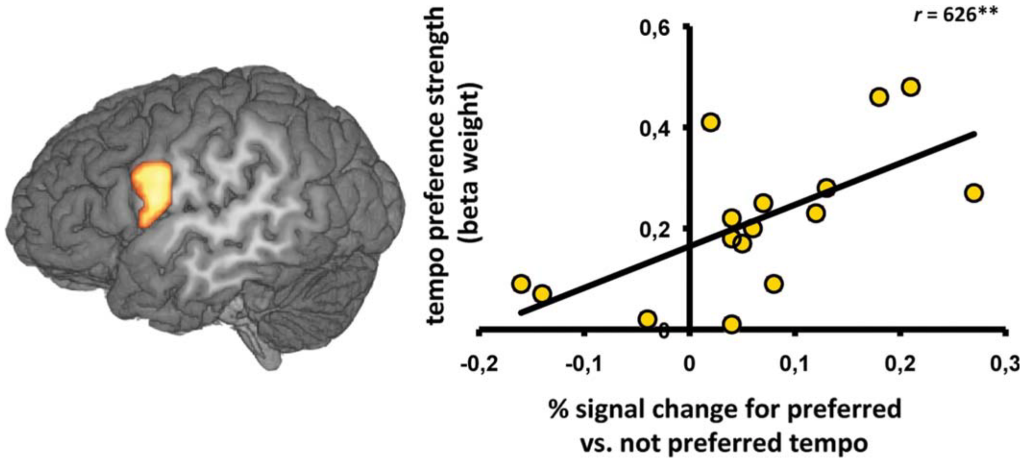

Figure 1.

fMRI findings leading to the hypothesis of the present rTMS study. A preceding fMRI study [Kornysheva et al., 2010] revealed that left ventral premotor (PMv) activity was enhanced for musical rhythms with a preferred beat rate (tempo). This signal increase significantly correlated with the subjects' individual tempo preference strength. Despite these results, it remains an open question whether interference with activity in the left PMv affects tempo preference strength. If this were the case, an inhibitory stimulation of the left PMv should demonstrate a temporary reduction of tempo preference strength which correlates positively with the subject's baseline tempo preference strength. That is, the effect should be stronger in those subjects who tend to show a larger activity increase in the left PMv when its activity is not affected by rTMS.

Despite the evidence for a coupling between preferred auditory tempo and movement, it is not fully understood how the central nervous system drives the preference strength for auditory beat rates, i.e. whether activity in motor-related regions contributes to this preference. Neuroimaging studies have provided evidence that subjectively pleasurable music is accompanied by activity increase in medial and lateral motor-related cortical regions—the supplementary motor area (SMA) and the Rolandic operculum, as well as the cerebellum [Blood and Zatorre, 2001; Koelsch et al., 2006], but these studies did not directly examine the link between these regional activity increases and the preference for specific rhythmic components, such as preferred auditory rhythm or beat rate. To investigate whether preferred tempo, a component considered to be most elementary with respect to coupling sound to movement [Cross, 2001; Janata and Grafton, 2003], leads to an activity increase in motor-related sites, we recently conducted a magnetic resonance (fMRI) study involving rhythmic musical patterns [Kornysheva et al., 2010]. On the basis of the subjects' individual aesthetic judgments, the analysis of the BOLD-response revealed an activity boost in premotor and cerebellar areas during the subjective appreciation of musical rhythms. Specifically, left ventral premotor (PMv) activity was enhanced for stimuli with a preferred tempo, but not for stimuli with preferred timbre (control variable). Furthermore, there was a significant correlation between the subjects' tendency to prefer a tempo (be it slow or fast) and the signal increase in the left PMv (see Fig. 1). While these results demonstrated that an activity increase in the left PMv very systematically accompanies musical rhythms with a preferred tempo, they did not allow to draw conclusions with regard to the contribution of the left PMv to tempo preference. Is the left PMv coactivated with critical areas, but is itself not critical for tempo preference? Because of the observational nature of fMRI, it remains an open question whether activity in the left PMv directly contributes to tempo preference strength.

To directly address the contribution of left PMv activity on the strength of tempo preference, we conducted an off-line repetitive transcranial magnetic stimulation (rTMS) study. Low-frequency repetitive TMS is a noninvasive method which is applied in order to temporarily disrupt activity in a restricted cortical area by a transient reduction of cortical excitability [Boroojerdi et al., 2000; Chen et al., 1997; Gerschlager et al., 2001; Maeda et al., 2000]. It can provide insight into the causal role of a cortical area in behavior [Pascual-Leone et al., 2000], by showing that an interference with activity in this area can systematically affect behavior. Given that the signal increase in the left PMv correlated with the subjects' tendency to prefer a tempo, we hypothesized that PMv activity increase is not only associated with, but also affecting tempo preference strength. The influence of the variable tempo on their aesthetic judgment of the musical rhythms should temporarily decrease after inhibition of the left PMv and the stability of tempo preference should be transiently impaired.

In a randomly selected population, subjects considerably differ with regard to the strength of their tempo preference, with some subjects having no tempo preference at all and some subjects having a very strong tempo preference [Kornysheva et al., 2010]. Subjects with a stronger tempo preference had a more pronounced PMv activity boost during rhythms with preferred tempo than subjects with weaker tempo preference, some of the latter even showing an activity decrease during preferred tempo (see Fig. 1). Accordingly, we evaluated the effect of inhibitory stimulation depending on the individual tempo preference strength. If PMv activity influences tempo preference, an inhibitory stimulation of this region should have a more pronounced effect on subjects with stronger in contrast to subjects with weaker tempo preference, in whom activity increase in the PMv tends to be lower or missing. rTMS over the left PMv should produce a more pronounced effect in subjects with strong tempo preference since these are assumed to show a larger activity increase in the left PMv under normal conditions (see Fig. 1). A temporary disruption of activity in the left PMv should reduce the strength of individual tempo preference more strongly in subjects with a pronounced tempo preference in a control session.

To ensure that the expected effect is both region-specific, specific to the function under investigation and bound to PMv stimulation in time, we implemented four controls: First and based on the BOLD-contrast analysis of a preceding fMRI study [Kornysheva et al., 2010], the left temporo-occipital cortex/angular gyrus (AG) was chosen as a control site for stimulation. AG was significantly less activated (bilaterally) for all conditions containing auditory rhythms when compared to rest. Therefore, if the effect is specific to left PMv rather than just a region-unspecific influence of rTMS, the tendency to prefer a tempo shall be disrupted after left PMv stimulation, as compared to left AG stimulation (baseline). Second, the preference for a stimulus variable that is unrelated to timing within a sub-seconds range—timbre (spectro-temporal configuration of the sound)—served as a measure to probe the specificity of rTMS stimulation on tempo preference. Third, we included a condition which measured tempo recognition (probability to recognize rhythms with a fast beat rate) throughout the experiment, thus controlling for more basic perceptual capacities. Finally, to ensure that the effect is bound to PMv stimulation, we evaluated whether the effect is more pronounced in the first as compared to the second half of the experiment after PMv stimulation, since behavioral and neurophysiological effects of TMS are known to wear off across time [Allen et al., 2007; O'Shea et al., 2007].

METHODS

Subjects

Sixteen healthy female volunteers (mean age 25.1; range, 22–30 years) with normal or corrected to normal vision participated in the study. All subjects were right-handed according to the Edinburgh Inventory of Manual Preference [Oldfield, 1971]. None of them were professional musicians. Their rhythm perception ability ranged from 22 to 29 (mean, 26.6; SE, 0.58) on a scale of 30 (online version of the rhythm test from the Montreal Battery of Evaluation of Amusia (MBEA), http://www.delosis.com/listening/home.html). Therefore, each subjects was within two standard deviations of the population mean [Peretz et al., 2003; cf. MBEA norms update 2008, http://www.brams.umontreal.ca/plab/publications/article/57). One additional subject participated in the experiment, but her results were excluded from further analysis due to an incorrect measurement of the resting motor threshold (cf. TMS protocol). All subjects were naïve concerning the hypothesis of this study and encountered the stimulus material for the first time. None of the subjects had any history of medical or psychiatric disease or contraindication to TMS [Wassermann, 1998]. All subjects gave informed written consent to participate in this study. Experiments were approved by the Ethics Committee of the Medical Faculty, University of Cologne, Germany.

Stimuli and Tasks

Subjects were presented with auditory musical rhythms, which had five properties—tempo, measure (beat grouping), beat subdivision, rhythmic figure, and timbre—that varied orthogonally on two or three levels, respectively (see Fig. 2). These stimuli had been previously used and described in more detail in the abovementioned fMRI study [Kornysheva et al., 2010]. Two of these five properties were relevant for the current experiment: tempo (beat rate) and timbre (spectro-temporal configuration of the sound). Tempo was varied on three levels: slow (1.7 Hz/100 BPM), middle (2.0 Hz/120 BPM) and fast (2.5 Hz/150 BPM), whereas timbre could be either "wooden" (predominantly wooden drum instruments) or "metallic" (predominantly metallic drum instruments) with two versions of each timbre. The assignment of these timbre versions to experimental conditions and sessions was counterbalanced across participants. In combination with the other three counterbalanced properties of the musical rhythms (beat subdivision, beat grouping, rhythmic figure), the rhythms appeared in all 216 possible permutations, each rhythm presented only once per session.

Musical rhythms were used for aesthetic (AJ) and tempo (TJ) judgment conditions, which were also included in the preceding fMRI-study [Kornysheva et al., 2010]. The participants were instructed to attend to the presented stimuli and decide whether or not the presented stimulus was beautiful (AJ) or fast (TJ) (see Fig. 2). As demonstrated in a post-experimental interview of the abovementioned fMRI study, the German word for "beautiful", "schön", which also means "nice" and "pleasant", is closely related to liking the rhythms. The subjects were asked to judge the stimuli relative to other stimuli in the experiment and not relative to their favorite musical pieces. They were

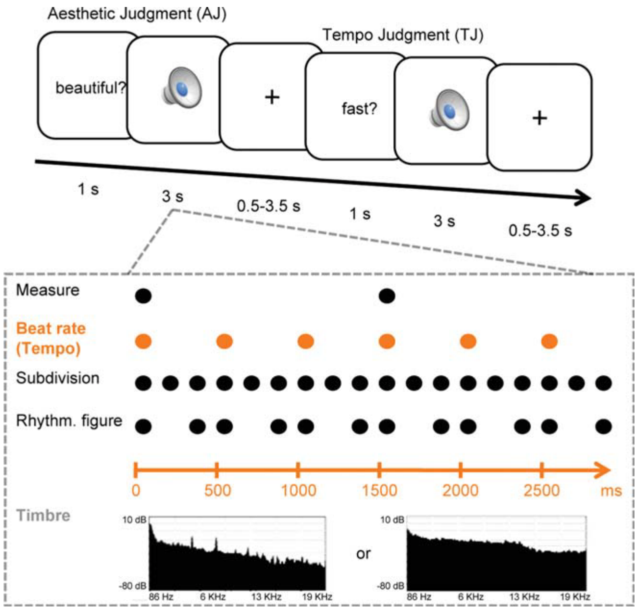

Figure 2.

Experimental trial and stimulus structure. Each trial started with a variable jitter time of 0.5–3.5 s followed by a task cue (1 s) and an auditory stimulus presented for 3 s. Subjects were asked to decide whether or not the presented stimulus was beautiful (Aesthetic Judgment) or fast (Tempo Judgment). Participants were asked to press the selected response button when they had decided but still while the sound was presented. The auditory stimulus was determined by five factors that varied on two or three levels, respectively: beat rate (tempo/inter-onset-intervals of beats), measure (grouping of beats), beat subdivision (elements per beat), rhythmic figure and a factor unrelated to subseconds timing - timbre (spectro-temporal configuration of the sound stimulus) (cf. sound examples in Supporting Information). Two of these five properties were relevant for the current experiment: beat rate (experimental variable in orange) and timbre (control variable in gray). The depicted rhythm example depicts a middle tempo with three beats per measure, three elements per beat and a repetitive rhythmic figure containing a long, followed by a short interval. The timbre panel shows two frequency spectrum types: sounds with predominantly wooden drum instruments (left side) and sounds with predominantly metallic drum instruments (right side).

instructed to press the button as soon as they decided while the rhythm was presented. Loudness was adjusted individually.

Each trial (6 s) started with a cue (1 s), indicating whether to perform an aesthetic judgment ("beautiful?") or a tempo judgment ("fast?"), followed by the stimulus (3 s) and a fixation phase the length of which was variable (0.5–3.5 s) depending on the jitter times (0, 500, 1,000, or 1,500 ms).

Since an inhibitory effect of rTMS usually does not outlast 20–30 min after the end of stimulation [Fitzgerald et al., 2006], the experiment lasted 21.6 min, during which 216 trials were presented: 108 in the AJ and the TJ condition, respectively. To capture a possible recovery of tempo preference strength after rTMS during this time range [Allen et al., 2007; O'Shea et al., 2007], all levels of tempo and timbre were equally distributed across the two sub-blocks (10.8 min each; Fig. 3) and conditions, respectively. We used 16 different trial randomizations matching the above criteria.

Procedure

Each subject participated in two sessions that were separated by seven days, with an exception of two subjects, whose sessions were separated by eight and ten days, respectively. During the session the subjects were tested after rTMS over either the left PMv or the left AG (see Fig. 3). The order of the sessions was counterbalanced across participants. The experiment took place in a quiet, shaded and air-conditioned room. Subjects were comfortably seated in an adjustable armchair with a head-rest. Each session started with a training containing example trials (12 trials AJ and 12 trials TJ), which were randomly

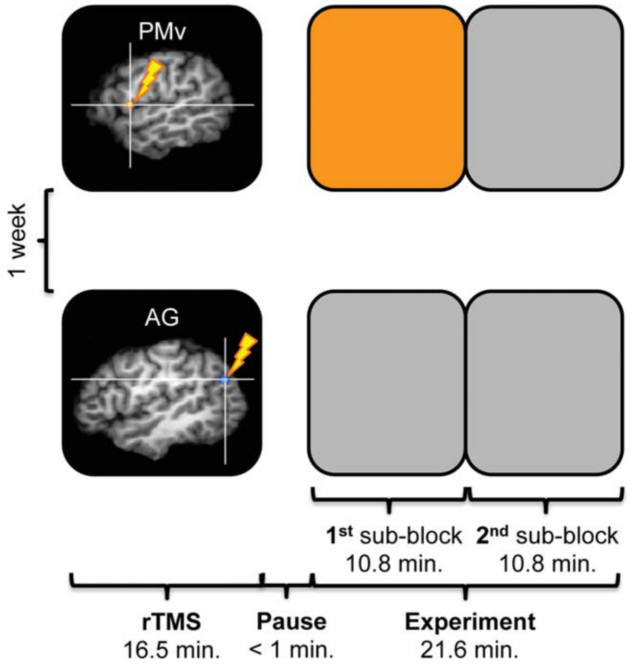

Figure 3.

TMS session procedure. Offline 0.9 Hz rTMS was performed over the left ventral premotor cortex (PMv) and over a control region (left temporo-occipital cortex/angular gyrus (AG)) in two separate sessions with an interval of one week. Each stimulation protocol was followed by a 21.6-min long experimental session that started within the first minute after stimulation. To capture a possible recovery of tempo preference strength after rTMS, the experiment consisted of two subblocks (10.8 min each).

chosen from the pool of stimuli for each subject and counterbalanced for tempo and timbre. This training had the purpose to familiarize the subjects with the task and the musical rhythms, as well as the range of tempos. It has been suggested that the effects of brain stimulation depend on the initial state of the stimulated region [Siebner et al., 2004] and may be influenced by psychophysiological manipulations such as priming [Silvanto et al., 2008]. When the level of excitation is high, a subsequent period of low frequency rTMS leads to a lasting reduction in excitability [Siebner et al., 2004]. Therefore, this training also served to potentially enhance activity in the respective network involved in tempo preference and tempo recognition prior to the application of inhibitory rTMS.

The subjects remained in the armchair after rTMS and were instructed not to talk during or after rTMS to minimize the interference of movement and speech with the hypothesized effect of the stimulation. The experiment started within the first minute after the administration of rTMS.

Site Localization

Stimulation targets were chosen on the basis of a preceding fMRI study [Kornysheva et al., 2010] conducted with a different group of subjects. The PMv site was defined by the peak voxel activated in the left lateral premotor cortex for musical rhythms judged as beautiful and for musical rhythms with a preferred tempo (overlap of the contrasts beautiful versus not beautiful rhythms and preferred versus not preferred tempo in the aesthetic judgment condition; Talairach coordinate: −50 4 12; cf. Fig. 2A, upper part). The control site (AG) was defined by the peak voxel activated in the left inferior parietal cortex for rest against all conditions involving musical rhythms (Talairach coordinate: −44 −68 30; cf. Fig. 2A, lower part). The distance of the TMS coil to the left ear was approximately the same for the two target sites, ensuring a comparable amount of exposure to the TMS noise prior to the experiment. None of the subjects reported a difference between the sessions with regard to TMS noise intensity.

An individual high resolution T1-image (3D MDEFT, data matrix: $256 \times 256 \times 128$) was acquired for each subject during a preceding scanning session. This 3D data set was transformed to Talairach stereotactic space [Talairach and Tournoux, 1988]. The respective contrast images from the preceding fMRI study were overlaid on each transformed individual 3D data set. The peak voxels were marked by crosshairs on the axial, coronal and sagittal planes, respectively. Subsequently, the stimulation targets were set manually on the T1-image according to the individual anatomical landmarks surrounding the crosshairs on the transformed 3D data set.

TMS Stimulation

Stereotaxic frameless neuronavigation was obtained by the eXimia NBS system Version 2.1.1 (Nexstim, Helsinki, Finland). Coil tilting was tangential to the skull and current direction was perpendicular to the central sulcus. Online neuronavigation was used to maintain the targeted tilting and direction of the TMS coil across stimulation.

TMS was applied with a biphasic Nexstim Eximia TMS with a figure-of-eight-coil (diameter: 50 mm). Motor threshold was determined at each session prior to rTMS in the right first dorsal interosseus muscle. Electromyographic (EMG) signals were recorded by surface electrodes placed in a belly-tendon montage over the target muscle. The EMG signal was amplified, filtered with a 0.5 Hz high pass filter and digitized using a PowerLab 26 T Myograph and the "Scope" software package Version 3 (ADInstruments Ltd, Dunedin, New Zealand). The resting motor threshold (RMT) was assessed by means of the maximum likelihood method as suggested by Awiszus [2003]; TMS Motor Threshold Assessment Tool (MTAT) 2.0, Awiszus F & Borckardt JJ, Brain Stimulation Laboratory, Medical University of South Carolina, USA, http://www.clinicalresearcher.org/software.htm), which has been suggested to be more accurate with the same number of stimuli [Awiszus, 2003; Awiszus et al., 1999; Mishory et al., 2004] in comparison to techniques proposed by Rossini et al. [1994], Rothwell et al. [1999] or Mills and Nithi [1997]. Peak-to-peak amplitudes exceeding 50 μV were regarded as motor evoked potentials.

Stimulation intensity was 90% of individual resting motor threshold (RMT), with a mean stimulation intensity of 37.8% (1.7% SE) of maximum stimulator output in the PMv and 39.0% (1.7% SE) in the AG session, the difference between the sessions being not significant ($t = -0.977$; $P = 0.344$, paired *t*-test). There was a significant correlation between the RMT in the two sessions ($r = 0.74$; $P < 0.01$). For each of the sites stimulated, 900 pulses were applied at a frequency of 0.9 Hz (train duration 16.5 min). A stimulation frequency slightly below the standard 1-Hz stimulation was chosen to exclude potential interference of rTMS noise with the 2 Hz beat rate of the musical rhythms in the subsequent experiment (cf. Stimuli and Tasks).

Side Effects of TMS

All 16 subjects reported muscular twitches in the left part of the face during the offline administration of rTMS over the left PMv. In contrast, only six subjects reported muscular twitches in the left part of the face during the offline administration of rTMS over the AG. At the end of the session with rTMS over the left PMv, one subject reported on a scale of 0 ("no") to 10 ("worst possible") a mild headache (2) and another subject reported a mild neck pain (1) in combination with a light nausea (1). At the end of the session with the administration of rTMS over the left AG two subjects reported a minor headache (3) in combination with a neck pain (2 and 5) and another subject reported light nausea (1). Prior to the session, the experimenter explicitly pointed out to each subject that they were free to terminate the stimulation or the experiment anytime as desired.

However, no subjects terminated or paused the stimulation or the experiment, indicating that the above side-effects were not experienced as very pronounced. No other side-effects were reported by the subjects.

Behavioral Analysis

For each individual participant, a linear mathematical model (individual case model) of judgment strategy was computed to examine the influence of the stimulus properties tempo and timbre on aesthetic judgments [Brehmer and Joyce, 1988; Cooksey, 1996; Jacobsen, 2004; Jacobsen et al., 2006; Kornysheva et al., 2010]. To this end, multiple regressions were computed using the enter method, including tempo (slow = "1", middle = "2", fast = "3") and timbre ("wooden" = "1", "metallic" = "2") as potential predictors of individual performance in the aesthetic judgment condition (AJ) of each session and subblock irrespective of the significance of their contribution. The latter, being nominal, was assigned "dummy" variables. The other three properties of the musical rhythms—measure or beat grouping, beat subdivision and rhythmic figure—were not included in the analysis. Note however, that the inclusion or exclusion of these properties as predictors in the regression (enter method) does not influence the results due to the orthogonality of all stimulus properties. This way, full models were computed to obtain the beta weights for the two predictors. These beta weights provided information on the mere tendency of every subject to prefer rhythms with slow (negative beta weights) or fast (positive beta weights) tempo, as well as rhythms with the timbre "wooden" (negative beta weights) or "metallic" (positive beta weights). The absolute value of beta weights for each session, as well as for each sub-block after rTMS was taken to reflect the strength of this preference [Kornysheva et al., 2010]. For example, a subject would be given a high beta weight for tempo whenever the number of positive aesthetic judgments of rhythms with slow tempo exceeded the number of positive aesthetic judgments of rhythms with middle tempo, and the latter, in turn, exceeded the number of positive aesthetic judgments of rhythms with fast tempo, or the opposite direction. In contrast, the subjects gained a low beta weight, whenever the number of positive aesthetic judgments of rhythms with slow, middle and fast tempo was approximately equal.

The effect of inhibitory stimulation on tempo preference strength was evaluated by taking individual preference strength into account. Individual tempo preference strength was treated as a continuous variable, since inhibitory stimulation of the PMv should have a more pronounced effect on subjects with stronger preference, i.e. subjects who have been shown to have a greater PMv activity boost during rhythms with preferred tempo than subjects with no or weak tempo preference [Kornysheva et al., 2010 and Fig. 1). The following correlation analyses were computed using standard Pearson's correlation coefficient and significance to probe whether the effect of rTMS over the PMv (i) positively correlates with the individual tempo preference strength in the control session and (ii) whether this effect is transient, i.e. temporally bound to rTMS stimulation. To control for the functional specificity of this effect, the same analyses were performed for timbre preference (control variable), as well. Correlations between preference strength in the control session (beta weight following AG stimulation) and the behavioral effect of rTMS over the PMv (beta weight following AG stimulation minus beta weight following PMv stimulation) were computed. The behavioral effect of inhibitory PMv stimulation was analyzed for each of the two sub-blocks of 10.8 min following PMv stimulation.

Additionally, correlations between the preference strength for tempo in each sub-block of the PMv and control sessions were computed. These correlations were used to investigate whether the stability of tempo preference strength within and across sessions is transiently impaired by PMv stimulation. As in the analyses above, the same correlations were also performed for timbre preference in order to evaluate the functional specificity of this effect. One-tailed correlations were used for experimental and control variables, since the hypotheses were unidirectional.

Individual tempo recognition during the tempo judgment condition (TJ) was computed for each session, as well as for each sub-block after rTMS, respectively. The performance was measured by the probability to recognize musical rhythms with a fast beat rate—the probability of recognition $P(\mathrm{r})$ [Snodgrass and Corwin, 1988]. The $P(\mathrm{r})$ was defined as $P(\mathrm{r})$ = HITS - FALSE ALARMS = (number of fast rhythms judged as "fast"/number of fast rhythms) − (number of slow rhythms judged as "fast"/number of slow rhythms).

A linear regression with the effect of PMv stimulation on tempo preference strength (beta weight for tempo following AG stimulation minus beta weight for tempo following PMv stimulation) as dependent and the effect on tempo recognition as independent variable ($P(\mathrm{r})$ following AG stimulation minus $P(\mathrm{r})$ following PMv stimulation) was computed. This was done in order to test whether the hypothesized effect on tempo preference strength could be explained by a disruption of tempo recognition.

Finally, reaction times and response distribution in the aesthetic and tempo judgment tasks were analyzed to control for possible confounds of rTMS over the PMv on attention, motor output and judgment bias.

RESULTS

Preference Strength for Beat Rate (Tempo) and Timbre

As expected on the basis of previous findings [Kornysheva et al., 2010, cf. Supporting Information and Fig. 1), the judgment analysis revealed that subjects differed with regard to the strength of their tempo preference, i.e., to how strongly tempo influenced their judgments, with

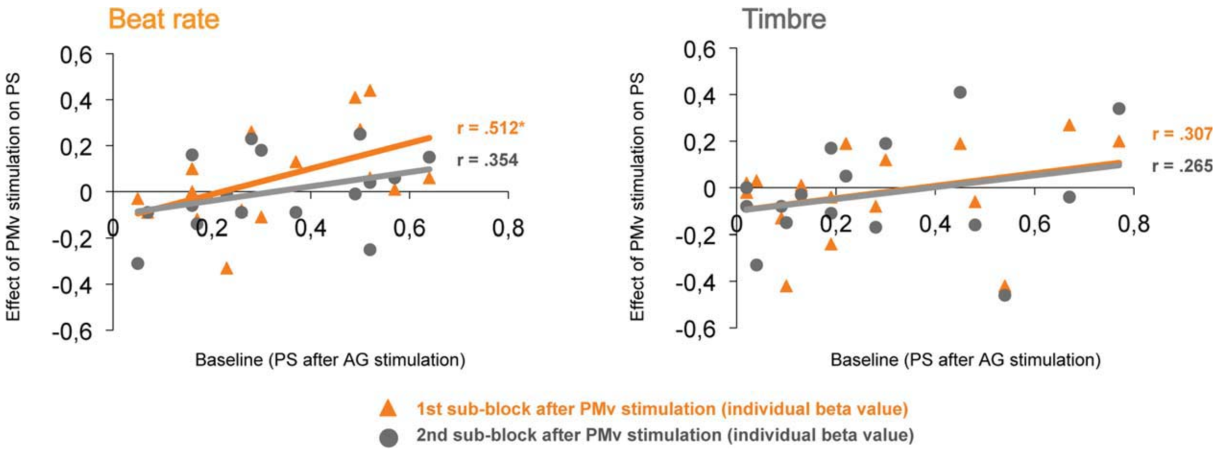

Figure 4.

Influence of left PMv stimulation on tempo preference strength. The effect of inhibitory PMv stimulation on beat rate preference strength (rTMS over the left PMv minus rTMS over the control site) covaried positively with the baseline beat rate preference strength. A significant correlation occurred only in the first sub-block following rTMS over the left PMv. No significant correlation was observed for timbre preference strength.

absolute beta weights ranging from 0.05 (no tempo preference) to 0.64 (strong tempo preference) in the control session (rTMS over the left AG). The beta weight for tempo did not reach significance in three out of sixteen subjects (beta weights ranging from 0.05 to 0.16). The reduction of tempo preference after PMv stimulation was driven by subjects with strong tempo preference in the control session (after AG stimulation; baseline). The higher the subject's individual tempo preference strength in the control session, the more tempo preference strength was impaired after PMv stimulation ($r = 0.473^*$; $P = 0.03$). This effect of PMv stimulation was transient, i.e. temporally bound to the first sub-block (first 10.8 min) after PMv stimulation: Tempo preference strength in the control session (baseline) and the effect of PMv stimulation on tempo preference strength correlated significantly in the first ($r = 0.512^*$; $P = 0.02$), as opposed to the second sub-block following PMv stimulation ($r = 0.354$; $P = 0.09$) (Fig. 4B, left part), consistent with an effect that wears off over time [Allen et al., 2007; O'Shea et al., 2007].

Serving as a control, the effect of PMv stimulation on preference strength for timbre was evaluated. As with regard to tempo preference, subjects differed in their preference strength for timbre, i.e. how strongly timbre influenced their judgments. Beta weights ranged from 0.02 (no timbre preference) to 0.77 (strong timbre preference) in the control session. The beta weight for timbre did not reach significance in six out of 16 subjects (beta weights ranging from 0.02 to 0.13). In contrast to the effect on tempo preference strength, a correlation analysis revealed that the effect of PMv stimulation on preference strength for timbre did not significantly increase depending on the individual preference strength for timbre in the control session, neither in the first sub-block ($r = 0.307$; $P = 0.12$), nor in the second sub-block ($r = 0.265$; $P = 0.16$) following PMv stimulation (Fig. 4B, right part).

In line with the above results, the stability of individual preference strength within and across the PMv and AG sessions was selectively impaired for tempo preference strength in the first, but not the second sub-block following PMv stimulation: While timbre preference strength remained stable within and across sessions the stability of tempo preference strength was affected in the first sub-block following PMv stimulation (Table I). This pattern of effects confirms that tempo preference suppression was transient and thus related to inhibitory PMv stimulation. Note, that the session order was counterbalanced across subjects. Accordingly, the observed effects of rTMS over the left PMv on tempo preference could not be related to whether the PMv stimulation was administered on the first or the second session.

Beat Rate Recognition

Importantly, the disrupting effect on tempo preference in the first sub-block after stimulation could not be explained by an impairment of basic temporal perception: In a linear regression analysis, the effect of PMv stimulation on tempo recognition (1st sub-block) did not significantly predict the effect of PMv stimulation on individual tempo preference strength (1st sub-block) ($R = 0.103$; $P = 0.71$).

Reaction Time

One subject had to be excluded from reaction time (RT) analysis, since the latency of one button was not recorded

TABLE I. Stability of preference strength for tempo and timbre (control variable) within and across sessions

		PMv		AG	
	Subblock	1st	2nd	1st	2nd
Beat rate preference strength					
PMv	1st				
	2nd	0.398			
		(0.06)			
AG	1st	0.302	**0.546***		
		(0.13)	(0.01)		
	2nd	0.389	**0.693****	**0.699****	
		(0.07)	(0.00)	(0.00)	
Timbre preference strength					
PMv	1st				
	2nd	**0.783****			
		(0.00)			
AG	1st	**0.644****	**0.568***		
		(0.00)	(0.01)		
	2nd	**0.563***	**0.488***	**0.654****	
		(0.01)	(0.03)	(0.00)	

Correlation matrix shows Pearson's correlation coefficients and significance values (in parantheses). Significant coefficients are in bold font. The stability of tempo preference strength within and across sessions was selectively impaired in the first sub-block following inhibitory PMv stimulation. Preference strength for timbre remained stable within and across sessions.

in the AG session. Mean response times and standard errors (in parentheses) in the AG session were as follows: beautiful (aesthetic judgment (AJ) "yes") 2,016 ms (78 ms); and not beautiful (AJ "no") 1,853 ms (87 ms); fast (tempo judgment (TJ) "yes") 1,513 ms (78 ms); and slow (TJ "no") 1,678 ms (81 ms). Mean response times in the PMv session were as follows: beautiful (AJ "yes") 2,076 ms (88 ms); and not beautiful (AJ "no") 1,848 ms (92 ms); fast (TJ "yes") 1,525 ms (77 ms); and slow (TJ "no") 1,677 ms (84 ms). A repeated-measures ANOVA over the judgment latencies with the factors ROI (PMv/AG), TASK (AJ/TJ), and TEMPO (slow/middle/fast) revealed a main effect of TASK ($F_{(1,14)} = 28{,}427$, $P < 0.001$) due to longer RTs in AJ trials, a main effect of TEMPO ($F_{(1,14)} = 25{,}847$, $P < 0.001$) due to longer RTs in trials with slow tempo. Notably, there was no main effect of ROI on reaction times ($F_{(1,14)} = 0{,}031$, $P = 0.86$), suggesting that attention and motor output was comparable during measurements following PMv and AG stimulation.

Response Distribution

Aesthetic judgment (AJ) showed 0.2% and tempo judgment (TJ) 0.1% non-responses. In the AG session, 45.4% of the stimuli under the aesthetic judgment task were judged as beautiful, 54.1% as not beautiful. In the PMv session, 42.5% of the stimuli under the aesthetic judgment task were judged as beautiful, 57.3% as not beautiful.

In the AG session, 53.5% of the stimuli under the tempo judgment task were judged as fast, 46.4% as not fast. In the PMv session, 50.5% of the stimuli under the tempo judgment task were judged as fast, 49.5% as not fast. There was neither a main effect nor an interaction with the factor ROI in a repeated-measures ANOVA over the percentage of judgments with the factors ROI (PMv/AG), TASK (AJ/TJ) and ANSWER ("yes"/"no"). There was a significant interaction of TASK and ANSWER due to the reduced fraction of answers "yes", i.e. "beautiful" in the AJ task compared with the fraction of answers "yes", i.e. "fast" in the TJ task ($F_{(1,15)} = 4{,}955$, $P < 0.05$).

DISCUSSION

This study was conducted to determine whether the preference strength for a musical beat rate (tempo) would be affected after inhibitory stimulation of the left ventral premotor cortex (PMv). We used 0.9 Hz repetitive magnetic stimulation (rTMS) to temporarily reduce cortical excitability in the left PMv and measured the strength of the subjects' individual tempo preference in the first 21.6 min after stimulation. To control for the regional and functional specificity of rTMS, the baseline measurement was performed after stimulation over the angular gyrus (AG) as a control site. Moreover, the preference strength for timbre and the overall tempo recognition were measured throughout the experiment. As hypothesized, rTMS over the left PMv compared with rTMS over the control site temporarily reduced the strength of individual tempo preference depending on how pronounced the tempo preference was in the control session. The disrupting effect of inhibitory left PMv stimulation correlated positively with the individual tempo preference strength in the baseline session, and wore off in the second part of the experiment following PMv stimulation. Likewise, the stability of tempo preference across the two sessions was impaired in the first sub-block after inhibitory PMv stimulation. Most importantly, both effects of rTMS over the left PMv were specific to the preference strength for tempo, whereas the preference strength for timbre, figuring as a control variable, was not affected. Finally, the effect on tempo preference strength was not related to a degradation of tempo perception itself.

Results suggest that a virtual lesion of the left PMv specifically interferes with the preference for beat rate as opposed to the preference for timbre, a timing-unrelated property of the musical rhythms employed here. These findings crucially extend the preceding fMRI results [Kornysheva et al., 2010] by showing that left PMv activity is affecting musical beat rate (tempo) preference.

It has been suggested that preference for a beat rate may be closely related to body movement. The tempo range of musical beat perception around 300–900 ms inter-onset-interval is similar to that of locomotion and other rhythmic movements [Fraisse, 1982; van Noorden and Moelants, 1999; Trainor, 2007]. Accordingly, anthropomorphic features that affect locomotion factors were shown to be correlated with the preferred beat rate [Todd et al., 2007]. In particular, the vestibular system, that is stimulated by head movement, has been suggested to be important with respect to beat preference: in both infants and adults active or passive movement (bouncing) compared with movement observation while listening to an ambiguous rhythm pattern has been shown to bias the perception of the ambiguous rhythm [Phillips-Silver and Trainor, 2005, 2007]. Moreover, in adults passive motion of the head alone affected auditory encoding, whereas passive motion of legs did not [Phillips-Silver and Trainor, 2008]. Evidence has been provided that a putatively homologous region of the human PMv in the macaque monkey sends direct cortico-fugal projections to the vestibular nuclei [Akbarian et al., 1993, 1994]. At the same time, in humans, vestibular input has been shown to enhance BOLD-activity in ventral premotor regions [Lobel et al., 1998].

Additionally, the anatomical position of PMv renders this area a node for auditory-motor integration: According to current accounts, auditory information is transferred to premotor areas via the superior longitudinal and the arcuate fasciculus (AF), which connect the superior temporal and the inferior parietal lobe with the lateral precentral gyrus [Bernal and Ardila, 2009; Rilling et al., 2008; Saur et al., 2008]—the so-called dorsal auditory stream [Hickok and Poeppel, 2004, 2007; Rauschecker and Tian, 2000]. A recent cortico-cortical evoked potential study has found that AF transmits information bidirectionally, i.e. also from precentral back to temporal and parietal regions [Matsumoto et al., 2004]. These results challenge the traditional notion of a mono-directional posterior (auditory) to anterior (motor) flow of information of the AF [Geschwind, 1970], but advocate the claim that motor information is important for perception, as pointed out with respect to language [Liberman et al., 1967; Liberman and Whalen, 2000]. Moreover, they are in line with findings demonstrating the influence of the motor on the sensory system by means of a corollary discharge or efference copy [Sperry, 1950; von Holst and Mittelstaedt, 1950], such as from the motor to the auditory systems in humans [Paus et al., 1996] and insect models [Poulet and Hedwig, 2006], as well as from motor to tactile [Blakemore et al., 2000, 1998] and from motor to visual systems [Wurtz, 2008]. At the same time, the left PMv sends direct corticospinal outputs and projects to left primary motor cortex [Dum and Strick, 1991, 2002], as well as to its right homologue, the right PMv [Dancause et al., 2007].

In line with these anatomical findings, the PMv has been shown to be relevant for sensorimotor integration of auditory beat cues. Imaging studies revealed enhanced activation in PMv during the synchronization of finger tapping to an auditory beat [Jancke et al., 2000; Rao et al., 1997; Thaut, 2003]. In contrast to the supplementary motor area (SMA), the PMv is specifically involved in the presence of externally cued beat. Studies, in which the underlying beat has to be internally generated on the basis of an auditory rhythmic structure (beat induction) have reported enhanced activation of the SMA and the putamen [Grahn, 2009; Grahn and Brett, 2007; Grahn and Rowe, 2009]. Accordingly, in a recent study, Grahn has demonstrated that internal beat generation is impaired in Parkinson's disease (PD) patients compared with controls [Grahn and Brett, 2009]. Moreover, a therapeutic effect of synchronization to an externally cued beat on gait and speech has been reported in patients with PD, suggesting that the lateral premotor cortex compensates the functional impairment of the basal ganglia-SMA loop during voluntary movement [McIntosh et al., 1997; Thaut et al., 1999; Thaut et al., 2001; Willems et al., 2007]. Malcolm et al. [2008] examined the influence of 0.9 Hz rTMS over the PMv on the synchronization of finger tapping to a 2 Hz auditory beat. However, despite the increase in synchronization error after the stimulation of the PMv, this effect was not significant. Future studies should evaluate whether the absence of a significant effect with regard to synchronization is due to an effective compensation of PMv dysfunction by interconnected areas.

Moreover, recent structural and functional neuroimaging, as well as TMS studies, highlighted the importance of PMv in audiomotor integration of speech. It has been shown that adolescent and adult subjects with stuttering show a lower fractional anisotropy of white matter tracts underlying the PMv compared with healthy controls [Watkins et al., 2008]. People with stuttering usually have expertise in using external timing cues like the pace of a metronome, other readers' speech in chorus reading, or altered auditory feedback to produce fluent speech [Alm, 2004; Buchel and Sommer, 2004]. It has been suggested that in the presence of external timing cues the lateral premotor cortex and the cerebellum compensate for the dysfunctional basal ganglia-SMA loop, which fails to generate or appropriately transmit valid internal timing cues for movement and speech in people with stuttering, similar to PD patients [Alm, 2004]. Thus, the reported structural abnormalities of white matter tracts underlying the lateral ventral premotor area may partly arise due to an altered gyrification of frontal and temporo-parietal areas in subjects with stuttering [Foundas et al., 2001]. Apart from speech production, the PMv has been demonstrated to contribute to speech perception as well. Meister et al. [2007] found that low-frequency rTMS over the left PMv significantly impaired phonetic discrimination.

Can the involvement of the premotor cortex in the strength of beat rate preference be linked to the common urge to spontaneously tune in to a musical beat by toe tapping, swinging of the upper body, head nodding or humming? When considering the anatomical position of PMv and its function in auditory-motor integration, it is likely that auditory and vestibular input during repetitive movements around 2 Hz shape PMv connectivity, e.g. during walking, or motor synchronization to a musical beat. This connectivity in turn should determine the extent to which auditory rhythms with a particular beat rate cause activity in the PMv and thus the strength of beat rate preference. If PMv activity increase during rhythms with a preferred beat rate modulates activity in primary motor regions, it may be conceived to also drive the urge to tune-in to a musical beat by head nodding, toe tapping, humming etc. Alternatively, PMv activity influencing beat rate preference strength may reflect a perceptual phenomenon that does not affect auditory cued motor output. To address this question, future studies should probe the contribution of PMv activity on (effector-independent) synchronization to an auditory beat. Likewise, it is still an open question whether PMv activity during rhythms with a preferred beat rate is involved in a better prediction and/or an enhanced motor imagery of movements to the beat.

The current results indicate that the interference with tempo preference after rTMS over the left PMv could not be explained by an impairment of a more basic perceptual capacity of beat rate recognition, since the latter remained unaffected by rTMS. Although preceding fMRI findings implied that tempo preference and recognition drew on overlapping neural resources [Kornysheva et al., 2010], the current results suggest that beat rate recognition is subserved by a degenerate set of areas. TMS- or stroke-induced impairment of premotor and motor cortices automatically causes increased activity in the unaffected contralesional hemisphere, which in turn inhibits the affected hemisphere [Ferbert et al., 1992; Grefkes et al., 2008]. Thus, it is possible that activity in the right PMv increased in response to TMS stimulation over the left PMv and successfully compensated for the disruption of left PMv activity during the tempo recognition task. This suggests that intact activity in the left PMv is not necessary for the tempo task. In contrast, the influence of tempo on the aesthetic judgments decreased after inhibitory stimulation of the left PMv. If an activity increase in the right PMv occurred, it still did not effectively compensate for this dysfunction. On the other hand, this dissociation may be driven by different task affordances with regard to the beat rate of musical rhythms. In the tempo in contrast to the aesthetic judgment condition, beat rate served as a primary cue. Tempo judgment relies on sensorimotor simulation of the external beat, whereas aesthetic judgment does not (cf. Kornysheva et al., 2010]. Thus, it is conceivable that a disruption of PMv activity selectively engaged compensatory mechanisms during the tempo, but not during the aesthetic judgment task. Future studies should evaluate whether tempo preference is driven by a lateralized premotor component.

The disrupting effect of inhibitory left PMv stimulation on tempo preference strength was positively correlated with individual tempo preference strength in the control session. This result is in line with the previous finding which demonstrated that left PMv activity boost during preferred tempo correlates with individual tempo preference strength (Fig. 1, Kornysheva et al., 2010]. Subjects with a stronger activity increase in the left PMv during preferred tempo exhibited a more pronounced tempo preference. Thus, an interference with activity increase in this region by low-frequency rTMS produced an effect that covaried positively with the subjects' baseline preference strength. Reducing cortical excitability in the left PMv by low-frequency rTMS demonstrated a stronger effect on these subjects.

The objective of this study was to test whether the left PMv activity affects tempo preference. Yet, it is feasible that other interconnected brain regions are equally critical for tempo preference. Since a TMS pulse can spread to connected sites, conditioning effects of rTMS may not be limited to the stimulated cortex, but give rise to functional changes in interconnected cortical areas [Lee et al., 2003; Paus et al., 1997], even when a stimulation intensity is below the individual motor threshold. Thus, it cannot be ruled out that rTMS over the left PMv additionally affected activity in interconnected cortical and subcortical regions. Future studies, in particular those that involve off-line, as well as concurrent TMS and neuroimaging [Driver et al., 2009], should therefore dissociate the critical contribution of areas interconnected with the left PMv to tempo preference and, moreover, address the interaction between these areas during rhythm with individually preferred and not preferred tempo.

In conclusion, the results substantiate the influence of the left PMv on tempo preference and corroborate the preceding fMRI results. On the basis of current and prior behavioral, anatomical and neuroimaging findings, future studies should address whether activity increase in a subset of neurons of the ventral premotor cortex, a node of audiomotor integration, influences the urge to move or hum to a musical beat.

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