THE AUDITORY SPACE IN THE MOTOR SYSTEM

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Abstract—Sensory events in the space around us trigger specific motor patterns directed toward or away from the spatial location of the sensory source. Spatially-defined sensorimotor associations are well-known in the visual domain but less so for the auditory modality. In particular no spatially-directed audio-motor association has been described for the upper limb. We tested the instantaneous directional tuning of the corticospinal system by means of single-pulse transcranial magnetic stimulation (TMS) over the left motor cortex in 16 healthy volunteers while at rest. We recorded the lateral accelerations of the TMS-evoked movement by means of an accelerometer placed on the forearm. Acoustic stimuli (pure tone frequency = 1000 Hz, duration = 50 ms) coming from 25 different directions lying in the axial anterior half-plane at the height of the participant's ears were played on earphones. The entire set of sound directions covered a span of 160 (±80 where 0 is the frontal direction) at a fixed azimuth angle. Six different intervals between sound onset and TMS (0, 25, 50, 100, 150 and 200 ms) were tested for each sound direction. Significant correlations were found between sound origin and TMSevoked arm accelerations only when TMS was delivered 50 ms prior to sound onset. We show the presence in the upper limb motor system of auditory spatial tuning. Sound information accesses the motor system at very short latency, potentially compatible with both a subcortical and a cortical origin of the response. The use of TMS-evoked accelerations allowed us to disclose a strict directional tuning in audio-motor associations. 2015 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: reaching, peripersonal space, sounds, colliculus, sensorimotor transformation, motor control.

INTRODUCTION

One basic component of animal behavior is the representation of the surrounding space in terms of reaching movements toward the origin of given salient stimuli (Colby and Duhamel, 1996; Rizzolatti et al., 1997). In humans the two main senses that code for extrapersonal space are vision and hearing. Accordingly, the human brain is endowed with wellknown visuo-motor and audio-motor mappings that transform extrinsic spatial coordinates into spatially-oriented motor acts. Visuomotor and audio-motor behaviors are well-documented in the ocular and cephalic motor systems (Lestienne et al., 1983; Sparks and Mays, 1983). In the upper limb, visuo-motor associations are similarly well-known. Indeed a whole cortical network is seemingly devoted to coding visual information in congruent reaching movements (Jeannerod et al., 1998; Battaglia-Mayer and Caminiti, 2002; Culham and Valyear, 2006). Conversely, audio-motor associations in the upper limb of humans remain poorly understood.

Some data are present in the literature suggesting that also auditory stimuli access the motor system in an automatic way similar to visual stimuli. First some works employed TMS to investigate the presence of covert motor patterns elicited by sounds presented around the hand. It was found that the proximity of the stimulus to the hand strongly modulated the corticospinal output (Serino et al., 2009; Avenanti et al., 2012; Finisguerra et al., 2014). The results were interpreted on the basis of the auditory stimulus being contained within the peripersonal space, thus eliciting motor responses, or outside of it, resulting in no modulation of corticospinal output. In the aforementioned works however no directional tuning of the evoked movement was found, in spite of a strong tuning of motor responses to radial distance of the stimulus from the hand. It should be noted that previous studies employed motor-evoked potentials (MEPs) as a measure of corticospinal excitability. This physiological variable however may have limited value in representing the features of evoked movements, especially if only a small number of different muscles is recorded

(Cattaneo, 2015).

In the present work we employed a different approach that is optimal for studying directional tuning in the motor system, i.e. the acceleration of the TMS-evoked movement in an arm-centered frame of reference. TMSevoked accelerations were recorded while subjects listened passively to sounds coming from several different directions. The motor cortex was probed with TMS at different time-points after the presentation of the sound to assess the chronometry of the neural events in the motor cortex following the entrance of acoustic information in the nervous system. The choice of the timing was limited to the first 200 ms given that many TMS studies on motor cortex excitability indicate that automatic bottom-up sensorimotor phenomena tend to occur at very early latencies from stimulus onset (Barchiesi and Cattaneo, 2013; Ubaldi et al., 2015; Borgomaneri et al., 2014; Borgomaneri et al., 2015). Data analysis was not carried out on actual raw acceleration values at each of the sampled time-points, but rather on statistical parameters that expressed the correlation between TMS-evoked accelerations and the direction of stimuli at every single time-point. The results show a striking directional tuning of the upper-limb corticospinal system to sound directions.

EXPERIMENTAL PROCEDURES

Twenty right-handed and normal-hearing volunteers with no contraindications to TMS (Rossi et al., 2009) (12 females, mean age: 32.2 years; SD: 3.63 years) participated in this study and provided written informed consent in accordance with the Ethics Committee of the University of Trento (protocol n. 2009-033). Participants sit comfortably on a chair with their head held still with a chin-rest incorporating an additional lateral headconstraint. Both their arms lay relaxed on the desk in front of them. An inflatable rectangular pad air filled was placed below the right arm in order to allow free movements. Participants wore earphones through which acoustic stimuli were delivered and were asked to keep eyes fixating in primary position for the whole duration of the stimulation session.

Acoustic stimuli

Single pure tones with frequency = 1000 Hz, duration = 50 ms dB = 70 dB were played by means of earphones. Each trial was characterized by a different spatial direction of the played tone. The set of tested sound-directions ranged between ±80, considering 0 as the direction in front of the participants. The whole set of sound directions was composed as follows: 0, ±5, ±10, ±15, ±20, ±25, ±30, ±35, ±40, ±45, ±50, ±55, ±80 as shown in Fig. 1, for a total of 25 different sound directions from 80 to +80. Sounds were filtered with HRTF coming from the CIPIC HRTF Database (Algazi et al., 2001). This database, freely available in internet (http://interface.cipic.ucdavis. edu/sound/hrtf.html), contains HRTF obtained from recordings in 50 individuals of the impulse response measurements collected over the sphere surrounding individuals' heads at 25 different azimuths and 50 different elevations. Convolving a sound with the binaural impulse responses obtained from the recording at a defined azimuth and elevation angle, the final sound used for the stimulation possess all the cues (ILT, IAD and others) representing the selected location. In particular, we used the two HRTF obtained from measurements from a KEMAR dummy head recorded respectively at an elevation of 34, at an azimuth angle of 65 and at an elevation of 34 and an azimuth angle of 65 so that the sound source appeared with respect to the subject's gaze direction at the same elevation but coming either from the left or right side. For similar methods see also (Leonardelli et al., 2015).

TMS

Participants received single-pulse TMS by means of a Magpro stimulator (Magventure, Skovlunde, Denmark) in biphasic stimulus modality produced via an MC-B35 coil (mean winding diameter of 36 mm). The coil was positioned on the left-hemisphere hand motor cortex and held in place by means of a mechanical support. It was oriented with the handle pointing laterally forming a 45 angle with the midline. Before starting the experiment the resting motor threshold (RMT) was calculated for the biceps brachii muscle, according to standard methods (Rossini et al., 1994). The singlepulse intensity was set to 120% of the RMT. The TMS pulse was delivered at different latencies following sound presentation, i.e. in each trial first the sound was presented and then the TMS was delivered. In our experiment we tested 6 different sound–TMS intervals for each sound direction: 0, 25, 50, 100, 150 and 200 ms. The inter-trial time was fixed at 4 s for a total duration of 20 min of the experimental session.

Acceleration recording

Acceleration of the right arm was measured by means of a three-axial accelerometer fixed on the superior part of the forearm about 5 cm distal to the elbow. The analog signal was acquired on three different channels, one for each axis, and digitized by means of a CED 1401 micro Mk-II unit (Cambridge Electronic Design, Cambridge, UK) at a sampling frequency of 4 kHz. The acceleration data were then downsampled and smoothed to 100 Hz by averaging consecutive data within time bins of 10 ms. Downsampling or low-pass filtering is a common procedure in pre-processing of kinematic data (Winter, 2009). Movement signals have relatively low frequencies and therefore any change in the rationale for data reduction to a sampling frequency of 100 Hz is that limb accelerations are slow signals with frequencies well within 50 Hz both during ballistic voluntary movements (Newton et al., 1996; Sainburg and Schaefer, 2004), involuntary movements such as tremor (Meigal et al., 2012) and during TMS-evoked movements (Barchiesi and Cattaneo, 2013). A window of interest of 200 ms after the TMS pulse was extracted from the acceleration recordings, consisting therefore in 20 sample points per trial. Note that the x axis was reading lateral accelerations of the forearm and produced negative values for leftward accelerations and positive values for rightward accelerations. Data were baseline corrected by subtracting from the 200 ms post stimulus the mean value of acceleration of the 100 ms pre-stimulus. This procedure is necessary because the accelerometer’s signal is sensitive to gravity and therefore minimal changes in the resting position of the forearm produce changes in the baseline value. Finally, note that given the averaging within 10-ms bins of the data, we referred from now on to each bin as its middle time value (for example, the bin containing the data between 30 and 40 ms is referred to as the 35-ms time point).

Processing of acceleration data and correlation analysis

Each participant underwent a single experimental block containing 300 trials. The trials were classified according to the interval between the sound onset and the TMS (6 different intervals) and the angle from which the sound originated (25 different angles). Each angle was repeated once for each sound–TMS interval so that 50 trials (each containing all sound directions twice) were associated with a single sound–TMS interval. For each participant, trials were grouped according the sound– TMS interval in 6 groups of 50 trials each. All further analyses were carried out within each of the sound– TMS intervals.

Each trial was characterized by a single angle of sound origin (a number between 80 and +80) and by 20 consecutive data samplings of acceleration corresponding to each time point from 0 to 200 ms. Within each sound–TMS interval we ran multiple (n = 20) Pearson’s correlation tests between the sound angle and the value of acceleration at a given moment. In other words, we took the 50 sound angles and correlated them with the 50 corresponding acceleration values at t = 5 ms, at t = 15 ms, at t = 25 ms and so forth for the whole set of 20 acceleration samplings. In this way, the data from the 50 trials were reduced to a single series of 20 Pearson’s r values. Each participant was ultimately characterized by a set of 6 (corresponding to the sound–TMS intervals) traces of 20 consecutive r-values. The data were to be interpreted in this way: positive r-values in a single subject indicated that at that given time point the acceleration was positively correlated with the sound angle, i.e. the arm accelerated toward the right side when sounds came from the right and the arm accelerated toward the left side when sounds came from the left. Vice-versa, negative values of r would indicate that the arm accelerated away from the sound source, irrespective from whether it came from the right or from the left side.

At this point we performed the main analysis, at the group level. Typically, r-values are not normally distributed, showing a negative skew (Fisher, 1915). Parametric analysis on r-coefficients requires normal distributions of the data, which is achieved by means of Fisher's r to z transformation. We therefore applied such transformation to every single value of r, according to the formula: $z = 0.5 * [\ln(1 + r)/\ln(1\ \ r)]$, which is generally referred to as inverse hyperbolic function. We will refer from now on to these quantities as r–z transformed correlation coefficient. The main a priori hypothesis to be tested was that r–z transformed correlation coefficients of the population significantly deviated from a mean value of 0 at a given time point. We therefore opted for multiple single-sample t-tests against the null hypothesis of mean $x = 0$. We therefore performed a total of $20 * 6 = 120$ multiple comparisons. The p-level threshold for significance was therefore set to $p = 0.05/120 = 0.00042$. A similar analysis was conducted on the signal from all 3 axes of the accelerometer.

EMG recording

Muscular activity of the biceps brachii was recorded by means of passive Ag/AgCl electrodes in a bipolar bellytendon montage. The analog EMG signal was then amplified 1000 by means of a CED 1902 amplifier (Cambridge Electronic Design, Cambridge, UK) and digitized by means of a CED 1401 micro Mk-II unit (Cambridge Electronic Design, Cambridge, UK) at a sampling frequency of 4 kHz. The EMG recording was triggered by the TMS pulse and recorded frames included 700 ms before and 300 ms after the TMS pulse. Recording and triggers were organized by the Signal software (Cambridge Electronic Design, Cambridge, UK) and stored on a PC for offline analysis. The EMG signal was acquired solely for the purpose of calculating the motor threshold in a proximal muscle and to have direct evidence throughout the experiment of effective corticospinal excitation by TMS, since the biceps muscle is not directly involved in the lateral forearm movements that we were interested in but rather in vertical forearm displacements (see discussion for an overview of intra- and extra-rotator muscles of the arm). We analyzed the MEPs by measuring peak–peak amplitudes in single trials and performed an analysis analogous to that done on accelerations and described in the previous paragraph. We computed the Pearson's r correlation coefficients between the MEP amplitude and the degrees of sound direction for each of the sound–TMS intervals. We applied r–z transformation and ultimately assessed whether MEP amplitudes significantly correlated with sound direction at the group level.

RESULTS

An example of raw acceleration recordings is provided in Fig. 2. None of the participants reported neither immediate nor delayed undesired effects of TMS and in general the procedure was well-tolerated. The full set of mean r–z transformed correlation coefficients and the relative p-values from the 3 accelerometer axes are shown in Tables 1–3. r–z transformed correlation coefficients from the y (antero–posterior accelerations) and z (vertical accelerations) axes were not significantly different from 0 in any of the t-tests at any of the timings. On the contrary, on the x-axis of the accelerometer (horizontal lateral accelerations of the forearm) we found data that were significantly different from 0 in a short interval between 120 and 140 ms from TMS and only when TMS was applied 50 ms from the stimulus onset (Fig. 3). To further represent the individual variability of the data, the single subjects' values of the correlation coefficients are represented in Fig. 4, limitedly to the significant condition of the 50-ms sound–TMS interval. The analysis on MEP amplitudes did not yield any significant result given that all p-values of the t-tests were above $p = 0.07$. As discussed in the last paragraph of the methods this negative result was expected.

DISCUSSION

The present findings describe for the first time in humans the presence of upper limb fast audio-motor mappings that are directionally tuned. According to previous literature the existence of an auditory-defined space in the upper limb motor system of humans is uncertain. Most automatic audio-motor associations that are behaviorally evident are non-spatially oriented. One form of audio-motor behavior in the upper limbs is the well-defined startle response, consisting in a stereotyped flexor pattern (Chokroverty et al., 1992) that can be observed predominantly in cranial, axial and proximal limb muscles. However, the audio-motor response recorded here is not compatible with a startle reflex for two reasons. Critically, the startle response is not spatially oriented. Second, the frequency of the stimuli used here would have caused very fast habituation of a startle reflex, therefore rendering it unapparent after the first few stimuli (Chokroverty et al., 1992). Another, less defined example of audio-motor behavior involving the upper limb in humans is that of rhythmic movements. In humans upper limbs tend to move synchronously with rhythmic sound patterns, but also this type of sensorimotor association is not defined in an extrinsic spatial frame of reference (Thaut et al., 1991; Repp and Penel, 2004; Ferronato et al., 2014). A more interesting series of findings show that audio-motor associations are present in the human brain along an axis that is orthogonal to the radial directions examined here, i.e. along the near-far axis. It has been found using event-related motor cortex TMS (with experimental setups similar to those implemented in the present experiment) that sounds originating in the peripersonal space enhance corticospinal excitability to distal hand muscles (Serino et al., 2009; Avenanti et al., 2012; Ferronato et al., 2014; Finisguerra et al., 2014). The critical distance between the sound origin and the subjects' hand was 60 cm.

One main advantage of the present work compared to the previous literature is the use of TMS-evoked movements rather than MEPs. TMS-evoked kinematics can reveal fine tuning of the corticospinal system to spatial directions compared to MEP recordings (D'Ausilio et al., 2014; Cattaneo, 2015) and therefore are an optimal tool to investigate the spatial directionality of covert motor plans within the motor system. This is especially the case for proximal movements such as reaching/pointing, similar to the movements that are investigated in the present experiment. Reaching movements, although resulting in displacements of the hand in space, occur mainly around the shoulder joint and are produced by contraction of shoulder muscles, the deltoid, the teres maior, the supraspinosus, the teres minor, the subscapularis and the infraspinosus. The latter three are in particular involved in the intra- and extra-rotation of the arm that ultimately produces the lateral accelerations of the forearm in the present setting. The three involved muscles have opposite actions but are located deeply and very close to each other. This makes selective EMG recording with surface electrodes of extra- or intrarotator muscles impossible due to cross-talk between muscles and volume-conducted potentials (Kimura, 1997; Staudenmann et al., 2010). Taken together, this combination of biomechanical and electrophysiological features renders the MEP approach not informative. The yield of information that can be obtained with TMSevoked accelerations on the contrary remains unaltered.

Two features of the audio-motor mapping described here deserve deeper discussion, the possible frames of reference in which the motor behavior is embedded and the very fast timing of the access of auditory information into the motor system. In the present experiment we kept the head, eyes and body position fixed with respect to the azimuth of sound directions, therefore we cannot define on the basis of the present data whether the response is coded in a hand-centered, body-centered or eye-centered frame of reference (Soechting and Flanders, 1992). Further experiments are required to better define this issue. The finding of directional tuning in the corticospinal system at 50 ms from sound onset is of considerable interest. First of all it should be noted that previous studies on audio-motor and visuo-motor responses found sensorimotor responses very early after sensory stimulation. The study by Serino et al. identified corticospinal activity 50 ms after sound onset, very similar to the present study (Serino et al., 2009). Another study, investigating visuo-motor coding of the near and far space found activity in the corticospinal system as early as 70–80 ms after appearance of an approaching visual stimulus (Makin et al., 2009). In the present dataset, the finding of such an early activity allows us first of all to exclude the contribution of voluntary movement, since voluntary audio-motor responses in the absence of startling stimuli are well above 100 ms from stimulus onset (Valls-Sole et al., 2008). Second, it provides some cues on where the response could be originated. Auditory information reaches the primary auditory cortex as early as 30 ms from stimulus onset (Liegeois Chauvel et al., 1994) ad early cortical components of auditory evoked responses, the so-called P1 response, have maxima of activity between 40 and 60 ms from stimulus onset (Celesia, 1976). Physiologically the response at 50 ms is therefore compatible with a very fast transcortical loop. However, our knowledge of the cortical representation of auditory space for reaching assume the presence of auditory maps in the posterior parietal (Cohen and Andersen, 2002) and premotor cortices (Graziano et al., 1999). Auditory information should reach the motor cortex through a very fast temporal–parietal–p remotor–motor pathway. One possible alternative to a trans-cortical pathway is that the descending volley evoked by TMS summates at the level of the spinal cord with a convergent descending volley independently evoked by auditory stimuli The origin of the auditory evoked activity would therefore be subcortical rather than cortical. Possible candidate structures at the origin of such activity would be either the inferior colliculus or the deeper layer of the superior colliculus, where also spatial auditory information is known to be represented. The tecto-spinal tract is known to produce mainly spatially-oriented behavior, but little information is available in humans on the anatomical extension of the tecto-spinal fibers to the cervical segments and in general on its connections with the motor neurons innervating the proximal upper limb. Would the timing of the sound–TMS interval of 50 ms be compatible with an interaction at the spinal level with a subcortical audio-motor reflex? We may take the startle reflex as a prototypical audio-motor reflex. We know that startle responses are recorded in shoulder muscles around 60 ms from the startling sound and therefore they access spinal motor neurons around 50 ms from the sound. The TMS-evoked corticospinal volley delivered at 50 ms arrives onto motor neurons around56–58 ms from sound onset. It is therefore physiologically possible that the cortical TMS-evoked response reaches proximal limb motor neurons together with a putative tecto-spinal pathway. However, the present data do not allow us to differentiate between a cortical and a subcortical origin of the response and further work in this direction is needed. What possible other confounds could influence the data? One simple explanation of the observed effects could be that the sequence of two spatially localized sounds (the audio stimulus and the TMS click) could by itself generate an arm movement directed toward the location of the first sound, irrespective of corticospinal activation by TMS. Though we cannot exclude the hypothesis with the present data, such an interpretation would anyway lead to the conclusion that spatially- oriented sounds produce automatic spatially-oriented behavior at very short latencies. Finally some comment should be made on the latency from TMS of the significant accelerations. Considering that typically MEPs in the proximal arm and shoulder occur well before 20 ms from TMS, 125 ms may seem a long delay, possibly unrelated to the TMS-evoked corticospinal volley. However, a complex series of electrical and mechanical events occur between the onset of the MEP and the actual forearm rotation. The MEP is electromyographic activity generated by the action potentials traveling along the sarcolemmal membrane. The electrical events in the muscle fiber however are coupled with mechanical shortening of the muscle, a time consuming process referred to as ‘‘electromechanical delay’’ which ranges in humanskeletal muscles between 50 and 100 ms (Cavanagh and Komi, 1979; Vos et al., 1990). The muscular tension that is developed must overcome the viscosity of the muscle itself and the friction of the joint. The extra- and intrarotation movements of the arm are generated by contraction of shoulder muscles (see above). Therefore, before we can record pointing movements of the forearm, the muscle tension developed by rotator muscles in the shoulder must be transmitted through both the shoulder and the elbow joints, thus adding further delay. Fig. 2 illustrates a sample of acceleration recordings and the corresponding MEPs. As explained above, the biceps brachii is not the muscle directly involved in producing the lateral forearm movements, however it can be used to estimate electromechanical delay in our protocol, which corresponds to around 60 ms. This given, it is not surprising that activity recorded at 125 ms from cortical stimulation is possibly a direct effect of the corticospinal volley evoked by TMS.

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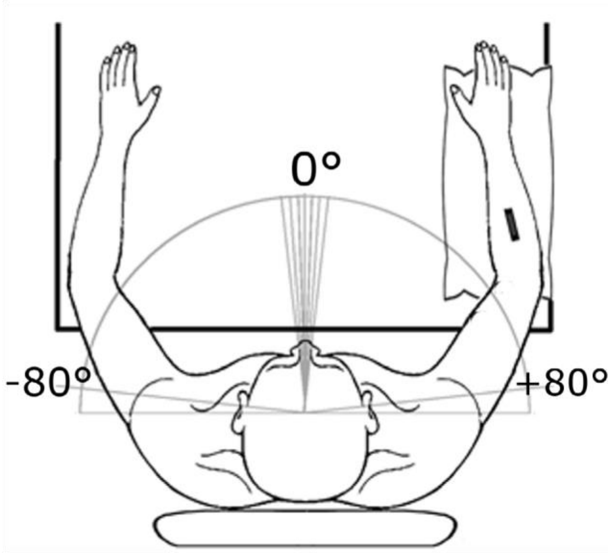

Fig. 1. Schematization of the sound directions with respect to the subject's head. The gray rectangle on the participant's forearm indicates the position of the accelerometer.

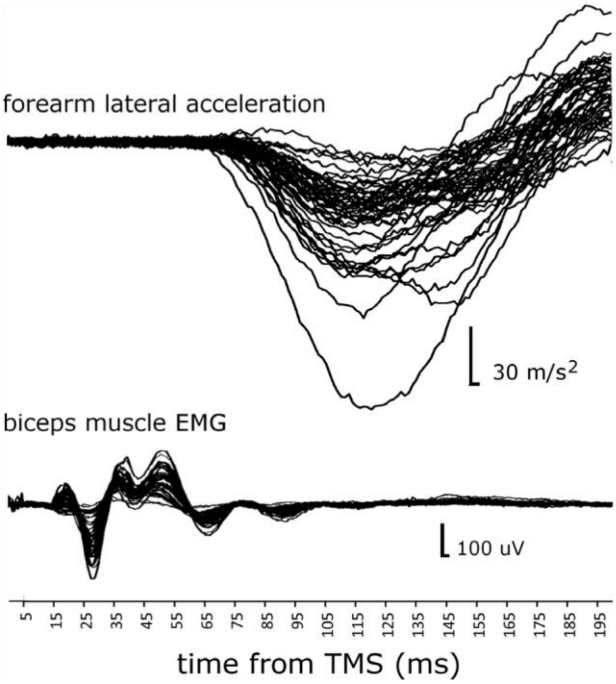

Fig. 2. Upper trace: example of raw acceleration recordings. The data from 50 trials from participant #8 are shown superimposed. Lower trace: superimposed EMG recordings from the biceps brachii from the same trials.

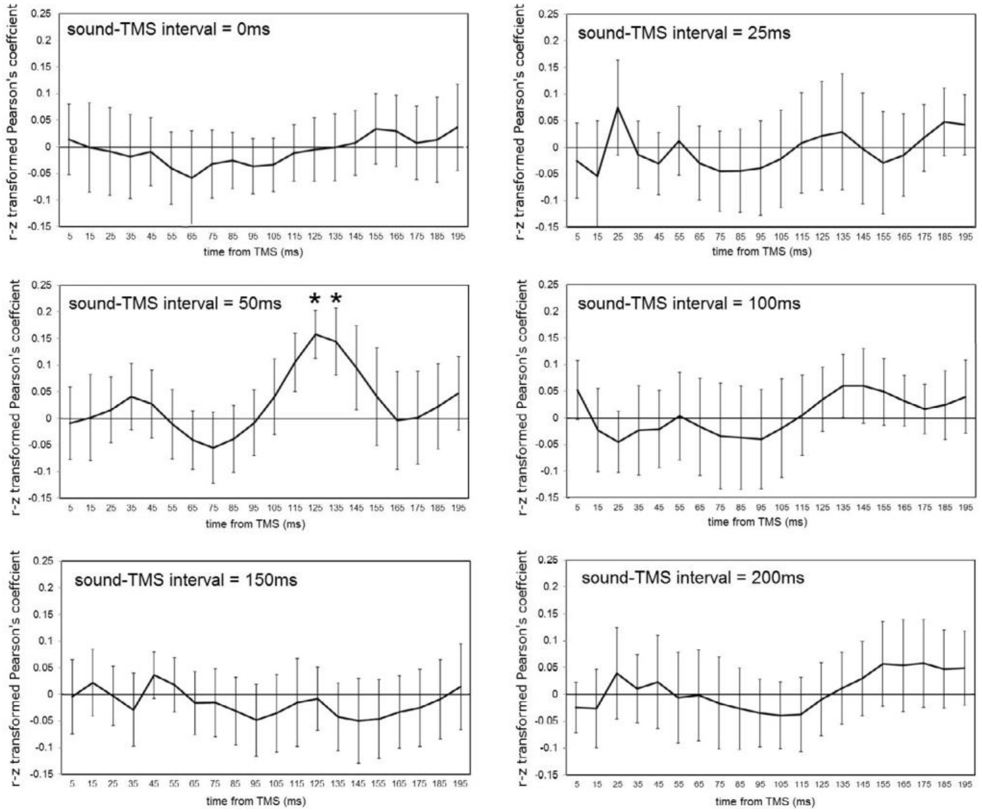

Fig. 3. Results from the x-axis (lateral accelerations of the forearm) of the accelerometer. The mean r–z transformed Pearson's r coefficients correlating the sound angle with the instantaneous acceleration are shown. Error bars indicate 95% confidence intervals of the mean. Asterisks indicate values of r–z coefficient significantly different from 0 (Bonferroni-corrected threshold for significance p = 0.00042).

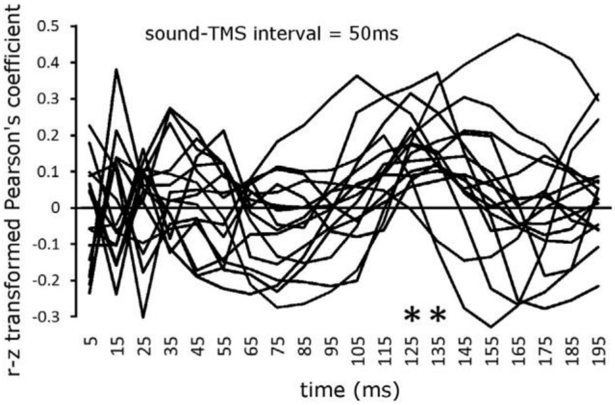

Fig. 4. Individual data of r–z transformed Pearson's r coefficients from the x-axis (horizontal accelerations) in the 50-ms sound–TMS interval (refer to the 3rd panel of Fig. 3 for average values). Asterisks indicate values of r–z coefficient significantly different from 0 (Bonferroni-corrected threshold for significance p = 0.00042).

Table 1. x-axis of the accelerometer (displacements of the forearm in the lateral direction) at different sound–TMS intervals, for each time bin of 10 ms. The numbers in the cells are: mean r–z transformed Pearson's coefficient (95% confidence interval of the r–z transformed coefficient's mean); p-value of the t-test against the null hypothesis of mean r–z transformed coefficient = 0. Note that following Bonferroni correction for 120 multiple comparisons, the threshold for significance has been set to p = 0.00042. Significant values of p are highlighted in bold

Time from TMS (ms)	Sound–TMS interval					
	0 ms	25 ms	50 ms	100 ms	150 ms	200 ms
5	0.0145 (0.066); 0.673	0.0249 (0.071); 0.545	0.0085 (0.068); 0.81	0.053 (0.056); 0.084	0.0038 (0.07); 0.917	0.0244 (0.048); 0.337
15	0.0008 (0.084); 0.985	0.0538 (0.105); 0.383	0.0022 (0.081); 0.958	0.023 (0.079); 0.576	0.0225 (0.063); 0.495	0.0264 (0.074); 0.495
25	0.0082 (0.082); 0.846	0.0756 (0.09); 0.165	0.0167 (0.062); 0.606	0.0453 (0.058); 0.148	0.0024 (0.056); 0.933	0.0401 (0.086); 0.377
35	0.0177 (0.079); 0.666	0.0135 (0.064); 0.718	0.0415 (0.062); 0.21	0.0233 (0.085); 0.599	0.0287 (0.069); 0.43	0.0113 (0.064); 0.734
45	0.0085 (0.064); 0.8	0.0303 (0.059); 0.382	0.0275 (0.064); 0.41	0.0208 (0.073); 0.586	0.0367 (0.044); 0.126	0.0235 (0.088); 0.608
55	0.0395 (0.068); 0.274	0.0127 (0.065); 0.733	0.0102 (0.065); 0.763	0.0038 (0.083); 0.93	0.0184 (0.051); 0.492	0.0058 (0.086); 0.897
65	0.0577 (0.088); 0.219	0.0296 (0.07); 0.47	0.04 (0.055); 0.173	0.0168 (0.092); 0.724	0.016 (0.06); 0.61	0.0014 (0.086); 0.975
75	0.0319 (0.064); 0.347	0.0449 (0.076); 0.316	0.0545 (0.067); 0.133	0.0341 (0.1); 0.514	0.0155 (0.064); 0.643	0.0162 (0.087); 0.72
85	0.0248 (0.053); 0.374	0.0439 (0.079); 0.347	0.0382 (0.063); 0.254	0.0371 (0.098); 0.47	0.0312 (0.064); 0.358	0.0266 (0.077); 0.51
95	0.0361 (0.052); 0.194	0.0389 (0.09); 0.462	0.0077 (0.062); 0.813	0.04 (0.094); 0.418	0.0484 (0.068); 0.18	0.0349 (0.064); 0.305
105	0.033 (0.05); 0.216	0.0213 (0.092); 0.691	0.0411 (0.071); 0.272	0.0192 (0.093); 0.691	0.0351 (0.073); 0.359	0.0392 (0.063); 0.243
115	0.0109 (0.053); 0.694	0.0083 (0.095); 0.879	0.1057 (0.055); 0.0018	0.0055 (0.076); 0.888	0.0151 (0.083); 0.725	0.0374 (0.07); 0.315
125	0.0045 (0.06); 0.885	0.0226 (0.103); 0.706	0.1588 (0.045); 0.000006	0.0355 (0.061); 0.272	0.0078 (0.06); 0.804	0.0091 (0.069); 0.798
135	0.0005 (0.063); 0.989	0.0298 (0.11); 0.64	0.1448 (0.063); 0.00041	0.061 (0.06); 0.065	0.0421 (0.064); 0.215	0.0117 (0.068); 0.742
145	0.0077 (0.061); 0.809	0.0022 (0.105); 0.971	0.0958 (0.079); 0.031	0.0609 (0.071); 0.114	0.0496 (0.08); 0.246	0.0301 (0.07); 0.416
155	0.0343 (0.066); 0.324	0.0287 (0.097); 0.611	0.0415 (0.092); 0.391	0.0497 (0.063); 0.143	0.0461 (0.075); 0.247	0.058 (0.08); 0.178
165	0.0304 (0.067); 0.387	0.0142 (0.078); 0.754	0.0032 (0.092); 0.947	0.0325 (0.048); 0.205	0.0329 (0.068); 0.361	0.0551 (0.087); 0.231
175	0.0081 (0.069); 0.821	0.0182 (0.063); 0.62	0.002 (0.087); 0.965	0.0172 (0.047); 0.483	0.0251 (0.073); 0.511	0.0589 (0.083); 0.187
185	0.0135 (0.08); 0.747	0.0488 (0.064); 0.205	0.023 (0.08); 0.58	0.0248 (0.065); 0.465	0.0088 (0.075); 0.822	0.0483 (0.074); 0.221
195	0.0373 (0.081); 0.383	0.0433 (0.057); 0.203	0.0478 (0.069); 0.196	0.0404 (0.069); 0.27	0.015 (0.081); 0.721	0.05 (0.07); 0.182

Table 2. y-axis of the accelerometer (displacements of the forearm in the anterior–posterior direction) at the different sound–TMS intervals, for each time bin of 10 ms. The numbers in the cells are: mean r–z transformed Pearson's coefficient (95% confidence interval of the r–z transformed coefficient's mean); p-value of the t-test against the null hypothesis of mean r–z transformed coefficient = 0. Note that following Bonferroni correction for 120 multiple comparisons, the threshold for significance has been set to $p = 0.00042$. Significant values of p are highlighted in bold

Time from TMS (ms)	Sound–TMS interval					
	0 ms	25 ms	50 ms	100 ms	150 ms	200 ms
5	0.013 (0.068); 0.715	0.004 (0.067); 0.909	0.0101 (0.067); 0.772	0.0137 (0.026); 0.309	0.0427 (0.072); 0.266	0.0166 (0.076); 0.673
15	0.007 (0.091); 0.882	0.0396 (0.068); 0.274	0.0314 (0.08); 0.453	0.0573 (0.079); 0.177	0.0386 (0.075); 0.329	0.0095 (0.083); 0.825
25	0.0259 (0.08); 0.537	0.0419 (0.071); 0.266	0.0349 (0.052); 0.208	0.0278 (0.065); 0.412	0.0404 (0.07); 0.274	0.0045 (0.09); 0.923
35	0.0005 (0.061); 0.987	0.0361 (0.063); 0.281	0.0204 (0.067); 0.56	0.0577 (0.059); 0.076	0.0425 (0.079); 0.309	0.0922 (0.079); 0.038
45	0.0211 (0.061); 0.505	0.0249 (0.069); 0.49	0.0375 (0.06); 0.243	0.0443 (0.043); 0.064	0.0394 (0.054); 0.175	0.0073 (0.097); 0.885
55	0.0404 (0.056); 0.177	0.0735 (0.062); 0.036	0.0282 (0.05); 0.288	0.0192 (0.059); 0.533	0.007 (0.064); 0.834	0.0135 (0.103); 0.8
65	0.0397 (0.068); 0.273	0.0395 (0.062); 0.23	0.0247 (0.045); 0.297	0.0236 (0.068); 0.506	0.0097 (0.076); 0.807	0.035 (0.117); 0.567
75	0.0395 (0.074); 0.314	0.0258 (0.062); 0.425	0.0119 (0.041); 0.577	0.0639 (0.076); 0.121	0.0389 (0.076); 0.334	0.0066 (0.113); 0.91
85	0.0332 (0.076); 0.405	0.0111 (0.06); 0.722	0.0141 (0.048); 0.578	0.0633 (0.08); 0.144	0.0371 (0.071); 0.324	0.0085 (0.099); 0.868
95	0.0367 (0.072); 0.332	0.0088 (0.057); 0.766	0.0195 (0.063); 0.555	0.0528 (0.091); 0.272	0.0119 (0.077); 0.766	0.019 (0.086); 0.671
105	0.0351 (0.067); 0.317	0.0369 (0.058); 0.229	0.017 (0.074); 0.66	0.0441 (0.096); 0.384	0.0081 (0.081); 0.847	0.0044 (0.079); 0.914
115	0.0108 (0.069); 0.763	0.0608 (0.06); 0.066	0.0031 (0.066); 0.927	0.0412 (0.093); 0.398	0.0292 (0.081); 0.489	0.0455 (0.068); 0.209
125	0.0124 (0.073); 0.744	0.0678 (0.071); 0.081	0.0181 (0.052); 0.501	0.01 (0.086); 0.824	0.0478 (0.08); 0.261	0.0636 (0.067); 0.082
135	0.022 (0.079); 0.595	0.0482 (0.081); 0.264	0.0221 (0.064); 0.509	0.0067 (0.092); 0.888	0.0439 (0.074); 0.266	0.0477 (0.071); 0.207
145	0.0032 (0.082); 0.94	0.0135 (0.08); 0.746	0.0002 (0.069); 0.996	0.0187 (0.1); 0.718	0.0393 (0.067); 0.271	0.0219 (0.081); 0.603
155	0.0141 (0.07); 0.701	0.0146 (0.079); 0.722	0.0157 (0.054); 0.58	0.0563 (0.096); 0.267	0.0645 (0.09); 0.181	0.0091 (0.076); 0.818
165	0.0168 (0.057); 0.574	0.0241 (0.072); 0.521	0.0166 (0.045); 0.48	0.0735 (0.08); 0.093	0.019 (0.101); 0.716	0.0123 (0.071); 0.74
175	0.0015 (0.057); 0.959	0.0098 (0.063); 0.766	0.0229 (0.051); 0.397	0.0755 (0.07); 0.052	0.0052 (0.098); 0.918	0.0329 (0.064); 0.327
185	0.0172 (0.069); 0.633	0.0324 (0.064); 0.334	0.0238 (0.063); 0.472	0.0782 (0.074); 0.056	0.0014 (0.089); 0.975	0.0607 (0.062); 0.075
195	0.0445 (0.08); 0.29	0.0448 (0.059); 0.157	0.0149 (0.065); 0.661	0.0868 (0.076); 0.04	0.0046 (0.073); 0.903	0.0756 (0.06); 0.025

Table 3. z-axis of the accelerometer (displacements of the forearm in the vertical direction) at different sound–TMS intervals, for each time bin of 10 ms. The numbers in the cells are: mean r–z transformed Pearson's coefficient (95% confidence interval of the r–z transformed coefficient's mean); p-value of the t-test against the null hypothesis of mean r–z transformed coefficient = 0. Note that following Bonferroni correction for 120 multiple comparisons, the threshold for significance has been set to $p = 0.00042$. Significant values of p are highlighted in bold

Time from TMS (ms)	Sound–TMS interval					
	0 ms	25 ms	50 ms	100 ms	150 ms	200 ms
5	0.0078 (0.07); 0.831	0.0118 (0.049); 0.64	0.0211 (0.072); 0.575	0.0105 (0.066); 0.761	0.0186 (0.072); 0.618	0.0267 (0.059); 0.385
15	0.0311 (0.082); 0.471	0.0055 (0.078); 0.892	0.0015 (0.103); 0.978	0.0585 (0.066); 0.104	0.0418 (0.067); 0.24	0.0183 (0.078); 0.652
25	0.0276 (0.064); 0.409	0.0006 (0.057); 0.984	0.0299 (0.073); 0.434	0.0345 (0.084); 0.433	0.0419 (0.085); 0.351	0.0079 (0.069); 0.825
35	0.0438 (0.066); 0.214	0.0104 (0.047); 0.67	0.0066 (0.054); 0.814	0.0085 (0.071); 0.817	0.0289 (0.09); 0.54	0.0846 (0.083); 0.064
45	0.0205 (0.058); 0.498	0.0473 (0.053); 0.102	0.0642 (0.067); 0.082	0.0484 (0.067); 0.179	0.0408 (0.062); 0.22	0.0428 (0.074); 0.273
55	0.0477 (0.053); 0.1	0.0622 (0.048); 0.022	0.0315 (0.084); 0.473	0.033 (0.06); 0.297	0.0638 (0.056); 0.04	0.0149 (0.088); 0.745
65	0.0312 (0.052); 0.254	0.0568 (0.053); 0.052	0.0107 (0.098); 0.833	0.0122 (0.077); 0.759	0.0402 (0.063); 0.232	0.0467 (0.095); 0.349
75	0.0166 (0.071); 0.654	0.063 (0.067); 0.086	0.0109 (0.092); 0.819	0.0001 (0.081); 0.998	0.0137 (0.053); 0.621	0.0309 (0.093); 0.524
85	0.0115 (0.071); 0.755	0.0628 (0.068); 0.092	0.0115 (0.082); 0.787	0.0053 (0.082); 0.9	0.0274 (0.05); 0.297	0.0265 (0.088); 0.565
95	0.002 (0.068); 0.954	0.0608 (0.067); 0.097	0.0221 (0.08); 0.598	0.004 (0.084); 0.928	0.0131 (0.062); 0.683	0.0331 (0.086); 0.46
105	0.0226 (0.071); 0.544	0.0519 (0.071); 0.175	0.0092 (0.072); 0.804	0.0065 (0.079); 0.875	0.0036 (0.083); 0.932	0.0053 (0.085); 0.903
115	0.0336 (0.077); 0.405	0.0293 (0.068); 0.409	0.0257 (0.06); 0.416	0.0145 (0.063); 0.661	0.0064 (0.087); 0.887	0.0296 (0.089); 0.526
125	0.0419 (0.074); 0.283	0.0089 (0.072); 0.812	0.0312 (0.05); 0.242	0.0361 (0.049); 0.169	0.0359 (0.084); 0.417	0.0456 (0.098); 0.378
135	0.0344 (0.065); 0.317	0.0337 (0.074); 0.386	0.0011 (0.071); 0.976	0.0224 (0.063); 0.494	0.0624 (0.086); 0.177	0.0252 (0.1); 0.63
145	0.0308 (0.062); 0.343	0.0253 (0.069); 0.485	0.0371 (0.078); 0.368	0.0119 (0.071); 0.747	0.064 (0.083); 0.153	0.0019 (0.105); 0.972
155	0.03 (0.085); 0.501	0.0161 (0.073); 0.671	0.0318 (0.062); 0.331	0.0049 (0.069); 0.891	0.0552 (0.083); 0.212	0.0112 (0.099); 0.827
165	0.0083 (0.087); 0.854	0.0219 (0.076); 0.582	0.0065 (0.053); 0.814	0.0001 (0.067); 0.998	0.0024 (0.084); 0.956	0.0379 (0.076); 0.344
175	0.051 (0.08); 0.232	0.0248 (0.08); 0.552	0.0378 (0.053); 0.182	0.0263 (0.058); 0.391	0.0245 (0.079); 0.551	0.0662 (0.05); 0.02
185	0.0513 (0.08); 0.23	0.0348 (0.076); 0.385	0.0774 (0.055); 0.015	0.0509 (0.07); 0.176	0.026 (0.074); 0.501	0.0668 (0.054); 0.029
195	0 (0.083); 1	0.0327 (0.073); 0.391	0.1032 (0.069); 0.01	0.0604 (0.067); 0.099	0.0123 (0.058); 0.685	0.0507 (0.06); 0.118