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RESEARCH ARTICLE

Modulation of steady-state auditory evoked potentials by cerebellar rTMS

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Abstract Steady-state auditory evoked responses (SSAER) obtained via electroencephalography (EEG) co-vary in amplitude with blood flow changes in the auditory area of the cerebellum. The aim of the present EEG study was to probe the cerebellar role in the control of such SSAER. For this purpose, we investigated changes in SSAERs due to transient disruption of the cerebellar hemisphere by repetitive transcranial magnetic stimulation (rTMS). SSAERs to click-trains of three different frequencies in the gamma-band (32, 40 and 47 Hz) were recorded from 45 scalp electrodes in six healthy volunteers immediately after 1-Hz rTMS and compared to baseline SSAERs assessed prior to magnetic stimulation. Cerebellar rTMS contralateral to the stimulated ear significantly reduced the amplitude of steady-state responses to 40-Hz click-trains and showed a tendency to reduce the amplitude to 32-Hz click-trains. No effects were observed for 47-Hz click-trains, nor for magnetic stimulation of the cerebellum ipsilateral to auditory stimulation or after sham stimulation. Our results suggest that interference with cerebellar output by rTMS modifies functional activity associated with cortical auditory processing. The finding of maximum effects on 40-Hz SSAERs provides support to the notion that the cerebellum is part of a distributed network involved in the regulation of cortical oscillatory activity and points at some frequency-specificity for the control of auditory-driven neuronal oscillations.

Keywords Steady state auditory evoked potentials · EEG · Repetitive TMS · Cerebellum

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Introduction

Oscillatory responses of the brain, induced by rhythmic stimulation of a sensory pathway (steady-state potentials), follow the stimulation frequency and show a peak response at around 40 Hz for the auditory system, as revealed both via electroencephalography (EEG) and magnetoencephalography (MEG) using trains of auditory clicks or frequency-modulated tones (Regan 1966; Stapells et al. 1984; Ross et al. 2000; Simpson et al. 2005). Also, when a tone modulated in amplitude at increasing frequencies or chirp is presented, the maximal energies in EEG are found at stimulation frequencies around 40 Hz (Artieda et al. 2004). The source of this steady-state auditory evoked response (SSAER) has been localized in the primary auditory cortex, supratemporal gyrus, and brainstem via EEG,

MEG and positron emission tomography (PET-H_2O^{15}) (Hari et al. 1989a; Makela and Hari 1987; Pantev et al. 1996; Gutschalk et al. 1999; Johnson et al. 1988; Herdman et al. 2002; Pastor et al. 2002; Simpson et al. 2005). In addition, using PET, the auditory area of the cerebellum has been found to be active specifically at 40 Hz, the auditory stimulation frequency that generates an SSAER of maximal amplitude and the maximum blood flow increment in auditory cortex (Pastor et al. 2002).

However, the mechanism leading to amplitude enhancement at around 40 Hz and the role of the cerebellum in the generation of the SSAER are unclear. Following the pioneering studies by Galambos et al. (1981), several investigators have advocated the notion that the 40-Hz SSAER represents the superimposition of individual transient middle latency auditory evoked responses, which add constructively at about 40–45 Hz and destructively at about 20–25 Hz (Hari et al. 1989b; Plourde et al. 1991; Stapells et al. 1988; Gutschalk et al. 1999). Other experiments suggested that the 40-Hz SSAER is merely the modal maximum across a group of subjects (Stapells et al. 1984). Another hypothesis argues that neural units have an intrinsic rhythm of firing that best resonates with a stimulus when it is presented at 40 Hz (Azzena et al. 1995; Basar et al. 1987; Santarelli et al. 1995). It has also been suggested that the SSAER could represent stimulus-induced phase resetting of ongoing field potential oscillations or reflect changes in the activity of neuronal assemblies (Makeig et al. 2002; Artieda et al. 2004). In a recent MEG-study, Simpson et al. (2005) were able to discriminate an amplitude component linearly related to the driving stimulus and a non-linear component related with input from other cortical areas. Finally, Pastor et al. (2002) have put forward a more connectionist account, suggesting that the cerebral 40-Hz SSAER might be controlled partially through the cerebellum at this auditory stimulation frequency.

In the present study, we sought to investigate whether transient disruption of the cerebellum will affect the scalp-recorded SSAER in normal human subjects. For this purpose, repetitive transcranial magnetic stimulation (rTMS) was combined with EEG. Single pulse TMS over the cerebellum decreases motor cortex excitability (Saito et al. 1995; Ugawa et al. 1995; Werhahn et al. 1996) and is able to modulate visually guided saccades (Hashimoto and Ohtsuka 1995) and smooth pursuit eye movements (Ohtsuka and Enoki 1998). Repetitive TMS at 1 Hz to the vermian area of the cerebellum is well tolerated and safe, and increases the variability of finger tapping movements in normal subjects (Theoret et al. 2001). We used 1-Hz rTMS and assessed SSAERs before and after (i.e., off-line to) magnetic stimulation. This form of slow rTMS is supposed to suppress activity in the targeted brain region beyond the duration of the rTMS-train itself (Robertson et al. 2003). Our hypothesis was that interference with cerebellar activity by 1-Hz rTMS would result in a decrement of synchronization and consequently of the amplitude of the SSAER generated in auditory cortex, with largest effect around the 40-Hz steady-state response.

Materials and methods

Subjects

Six healthy volunteers clinically screened for neurological or psychiatric diseases participated in this study (5 males mean age = 29 years, range = 19–36 years). All were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield 1971). They participated after giving written informed consent. The study had been approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center.

Auditory stimulus presentation

Subjects were seated comfortably in an armchair and were stimulated with a series of 640 ms click-trains (Fig. 1a) presented monoaurally through an earphone to their right ear. The rate of clicks within an auditory train was either 32, 40 or 47 Hz, and each click was of 1 ms duration. Trains of a given rate were repeated at

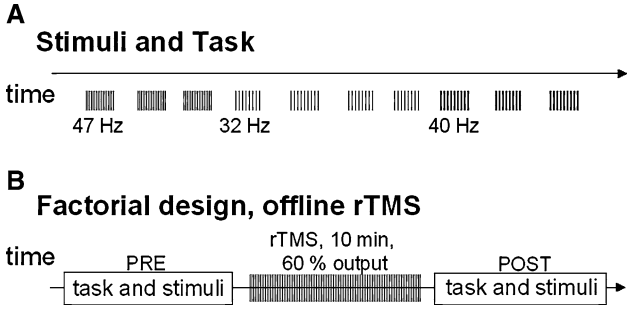

Fig. 1 **a** Subjects were stimulated with a series of 640 ms click-trains presented monoaurally at three different frequencies (32, 40, 47 Hz) through an earphone to their right ear. **b** Auditory stimuli were presented in blocks pre- and post-rTMS, i.e., prior and following a 1-Hz rTMS train of 10 min duration. In total, three TMS sites were tested (site 1–3). Each site of TMS-administration was repeated once and each post-rTMS block was followed by a 15 min break (washout period). TMS sites consisted of the left or right cerebellum (TMS Lt, TMS Rt) and involved a left cerebellar sham control (Sham Lt). The experimental design led to a 3 × 3 × 2 factorial design (FREQ × SITE × TMS)

least three and maximally six times in a row before switching to another rate. The order of the 32-, 40- and 47-Hz click-trains was pseudo-randomized and the inter-train interval was randomized from 200 to 500 ms. The subjects were asked to listen to the click-trains, to silently detect the changes in rate between trains, to keep their eyes open, and to avoid eye movements and blinks by fixating their gaze on a fixation point placed 2 m in front of them.

Auditory click-trains were presented in experimental blocks of 7.5 min duration each, giving rise to 150 repetitions per train frequency (32, 40 or 47 Hz) and block. A Power Mac computer (model: 9600/200, Apple Computer, Cupertino, CA, USA) running PsyScope (Macwhinney et al. 1997) was used for presentation of the trains.

rTMS protocol and design

The effects of real and sham rTMS on SSAERs were probed using an offline protocol and the following TMS parameters (frequency 1 Hz, duration 10 min, intensity 60% of maximum stimulator output). In the device we used, 60% maximum stimulator output typically corresponds to the resting motor threshold [$rMT_{right\ hand}$ mean = 60%, range 49–77%; obtained in a population of healthy subjects that participated in other studies ($n = 63$; age 20–38 years)]. We selected these parameters because they have been shown to bring about effects that outlast the duration of rTMS itself, i.e., (i) to lead to a reduction in cortical excitability (e.g., Chen et al. 1997; Boroojerdi et al. 2000; Muellbacher et al. 2000; Touge et al. 2001; Romero et al. 2002) and (ii) to a disruption of cognitive brain function beyond magnetic stimulation (e.g., Kosslyn et al. 1999; Hilgetag et al. 2001; Shapiro et al. 2001), as well as (iii) to affect EEG correlates of neural activity in a similar time range (Rossi et al. 2000; Schutter et al. 2001; Bohotin et al. 2002; Enomoto et al. 2001; Strens et al. 2002; Chen et al. 2003; Fumal et al. 2003; Thut et al. 2003). TMS-effects were assessed by comparing the SSAER recorded immediately after rTMS with those recorded at baseline, before rTMS (SSAERs in post- vs. pre-rTMS blocks).

Repetitive TMS was applied over the left or right cerebellum using an 11 cm double-cone coil (two real rTMS sites) as well as over the left cerebellum using a specially designed 7 cm figure-of-eight placebo (sham) coil (one sham rTMS site). The coil center was positioned 3 cm lateral to the inion at the level of the line joining the inion and the left or right external auditory meatus (for left or right cerebellar stimulation, respectively), in line with previous rTMS studies stimulating the cerebellum (Gerschlager et al. 2002). The target site of primary interest was the left cerebellum, because a previous PET-study found greater blood flow increase by 40-Hz auditory stimulation in the (left) cerebellar area contralateral to the stimulated (right) ear (Pastor et al. 2002). The right cerebellar site was included to test for differential effects of side of TMS. The left sham rTMS site served as control.

Each of the three different TMS-applications (left or right cerebellum or sham) was preceded and followed by a block of auditory stimulation (pre- and post-rTMS blocks, Fig. 1b), and was repeated once in order to increase the number of click-trains per train-type, TMS-site, and TMS-condition to $n = 300$. In addition, we introduced a break of 15 min following each post-rTMS block in order to allow washout of the rTMS-effects. Site of stimulation was counterbalanced across subjects over two experimental sessions that took place on two separate days. Each subject was tested in all conditions.

The experimental design led to a $3 \times 3 \times 2$ factorial design with frequency of click-trains (32, 40, 47 Hz), site (TMS Lt cerebellum, TMS Rt cerebellum, Sham Lt cerebellum) and TMS (pre, post) as factors.

TMS-apparatus, anatomical site of stimulation and EEG recordings

TMS was delivered by a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Dyfed, UK). Using optical tracking by a frameless stereotaxic system (Brainsight, Rogue Research, Montreal, Canada) and individual brain MR-images, we determined the anatomical site of stimulation offline to the experiment in the subjects (Fig. 2).

EEG was continuously sampled at 200 Hz during auditory stimulation from 45 standard locations according to the international 10–10 electrode system (Fpz, AF7, Afz, AF8, F3, F1, F2, F4, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P5, P3, P1, P2, P4, P6, PO7, POz, PO8, Oz). EOG was recorded through two additional bipolar horizontal and vertical derivations. To eliminate any risk of scalp burns due to overheating of the EEG contacts during TMS-exposure, non-polarizable, plastic-body electrodes coated with silver epoxy were used (Ives et al. 1991). EEG signals were recorded with a bipolar montage and were recalculated off-line against the average reference. Impedance was kept below 10 kΩ. A unit based on a 128-channel data acquisition system (Ives EEG solutions, Inc., Burlington, ON, Canada) originally developed for invasive EEG recordings (Ives et al. 1991) served for data acquisition.

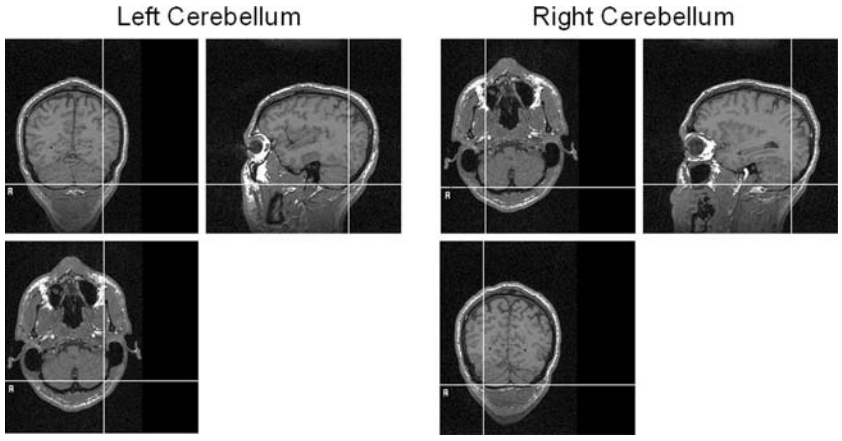

Fig. 2 The anatomical site of stimulation was determined offline to the experiment using optical tracking by a frameless stereotaxic system. The *cross-hairs* highlight the cortical point located radially inward from the center of the coil, projected onto individual MRIs

EEG analysis

EEG data were reorganized offline to the recording into 1,280 ms epochs aligned to the onset of the click-trains (−640 ms pre- to 640 ms post-stimulus onset, the post-onset period thus covering the duration of the click-trains). Single sweeps were carefully scanned for artifacts and if contaminated removed prior to the analysis. Approximately 250 artifact-free epochs were obtained per subject and condition.

In order to (a) determine the onset latencies and to (b) explore the dominant frequencies of the SSAER induced by the click-trains, EEG data were (a) averaged to auditory evoked potentials (1,280 ms epochs) and (b) Fourier transformed in the window overlapping the click-trains (640 ms-epochs, frequency resolution: 1.563 Hz) using Scan 4.2 software (NeuroScan Inc., Herndon, VA, USA).

To compute the amplitude of the SSAER in the time period following its onset, we applied a method for calculation of event-related band power changes, phase-locked to (i.e., evoked by) the click-trains (calculated via Scan 4.2 software). The phase-locking eliminates all the oscillations that were not strictly time-locked to the onset of the click-train, i.e., the oscillations in the pre-train window of 640 ms that ended with variable time-intervals before train-onset (Pfurtscheller and Lopes da Silva 1999). Changes in event-related band power (ERBP) were defined as the percentage of increase (or decrease) in band power following the onset of click-trains (0–640 ms post-stimulus onset) as compared to the reference interval (−640 to 0 ms pre-stimulus onset). Bandpass filters were set to 30–34, 38–42 and 45–49 Hz for steady-state responses to 32-, 40- and 47-Hz click-trains, respectively (12 dB/octave rolloff, trim left and right of 200 ms). The amplitude of the SSAER was then calculated by averaging over post-stimulus ERBP-values starting from the onset of the steady-state oscillations (175 ms post-stimulus, see results). This provided one amplitude value per condition and electrode.

Statistical analysis

Amplitudes of steady-state responses, as derived from the event-related band power (ERBP) algorithm, were compared between conditions for each electrode separately using $3 \times 3 \times 2$ analysis of variance (ANOVA, repeated-measure) with within-subject factors frequency of auditory stimulation (FREQ), site of magnetic stimulation (SITE) and TMS (Pre vs. Post). Since we expected rTMS-effects on SSAER to depend on both TMS-site and frequency of click-trains, based on previous findings of lateralized cerebellar activation specific to 40-Hz auditory stimulation (Pastor et al. 2002), we focused on the three-way interaction FREQ $\times$ SITE $\times$ TMS, mapped on the electrode array, and subsequent simple tests.

Results

Figure 3 depicts the auditory evoked potentials induced by 32-, 40-, and 47-Hz click-trains (grand-average) of pre-TMS trials (baseline blocks) in an exemplar lead contralateral to auditory stimulation (over left temporal cortex) as well as the corresponding frequency spectra in the period overlapping the click-train. Oscillatory electrical signals cycling at the stimulation frequency (steady-state response, SSAER) started to develop at around 150–200 ms post-stimulus onset (Fig. 3a) with similar amplitudes for 32-, 40- and 47-Hz click-trains (Fig. 3b).

Figure 4a illustrates the spatial distribution of those rTMS-effects on SSAER amplitude, which depended on both frequency of auditory stimulation and site of

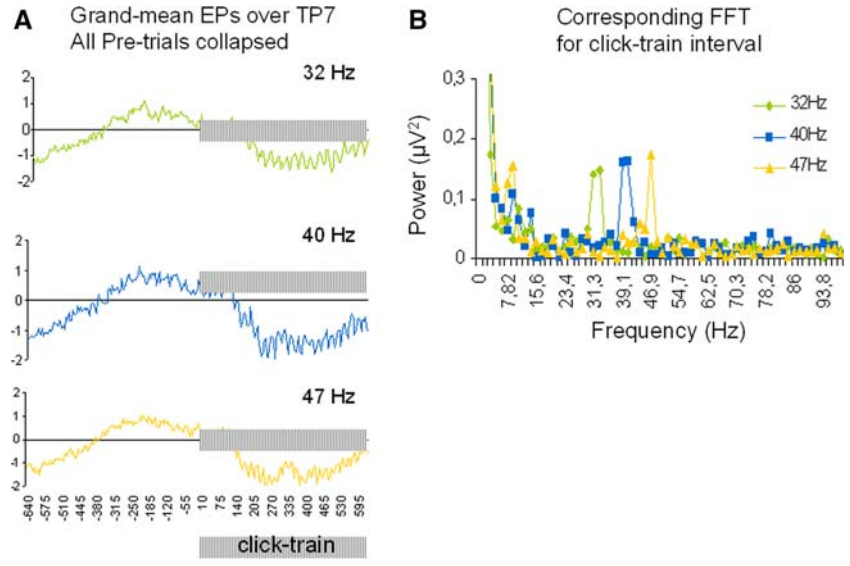

Fig. 3 **a** Auditory evoked potentials induced by 32-, 40-, and 47-Hz click-trains (grand-average of pre-TMS blocks) in an exemplar lead contralateral to auditory stimulation (TP7), as well as **b** the corresponding frequency spectra in the period overlapping the click-train (0–640 ms)

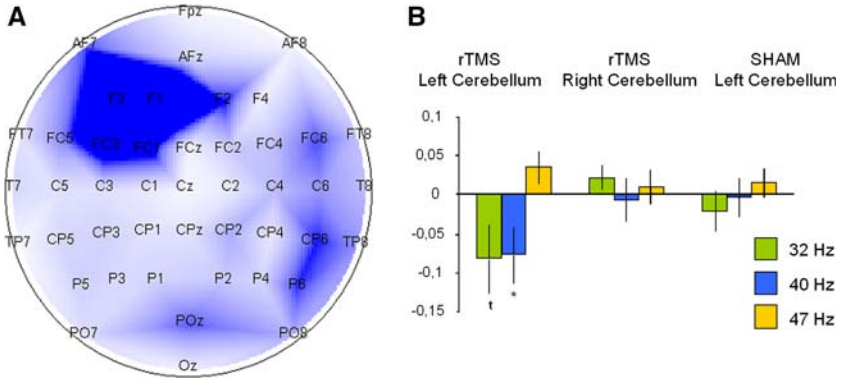

Fig. 4 **a** Spatial distribution of those TMS-effects on SSAER amplitude, which depended on both frequency of auditory stimulation and site of magnetic stimulation (*F*-values of the three-way interactions FREQ × SITE × TMS mapped on the electrode array). **b** TMS-induced changes in SSAER-amplitude (difference values, post-rTMS minus pre-rTMS block) at the left frontal contacts showing a significant three-way interaction (data collapsed over F1, F3, FC1 and FC3), as a function of frequency of auditory stimulation and site of magnetic stimulation. Negative values correspond to an SSAER-amplitude decrease in the post-rTMS block relative to baseline (pre-rTMS block). Between-subject averages (mean ± SE) are shown. * $P < 0.05$, t $P = 0.095$

magnetic stimulation (*F*-values of the three-way ANOVA interactions FREQ × SITE × TMS mapped on the electrode array). Significant *F*-values were obtained for left frontal electrodes F1 ($F = 6.2$, $P = 0.002$), F3 ($F = 4.7$, $P = 0.008$), FC1 ($F = 3.1$, $P = 0.04$) and FC3 ($F = 3.6$, $P = 0.02$).

Figure 4b depicts the difference in steady-state amplitude induced by rTMS (post-rTMS block minus pre-rTMS block, negative values correspond to an amplitude decrease) as a function of frequency of auditory stimulation and site of magnetic stimulation for the left frontal electrodes showing significant *F*-values (data collapsed over F1, F3, FC1 and FC3). Left cerebellar rTMS significantly reduced the amplitude of steady-state responses to 40-Hz click-trains ($P < 0.05$) and showed a tendency to reduce the amplitude to 32-Hz click-trains ($P = 0.095$). No effects were observed for 47-Hz click-trains, nor for stimulation of the right cerebellum or the left cerebellar sham control.

Discussion

Cerebellar rTMS at a frequency of 1 Hz produced a significant decrement in the amplitude of the SSAER. This effect was observed only when magnetic stimulation was administered over the cerebellar hemisphere contralateral to the stimulated ear and depended on auditory stimulation rate. Significant changes were observed for the 40-Hz SSAER and a trend was observed for the 32-Hz response, i.e., SSAERs in the lower gamma frequency range were affected by rTMS.

This result is consistent with PET-findings (Pastor et al. 2002) revealing asymmetric, frequency-specific activation of the cerebellar cortex during steady-state auditory stimulation, and thus provides further support to the notion that the cerebellum is part of the distributed neural network involved in the generation or control of SSAERs.

We found the effect of rTMS on SSAER-amplitude to be restricted to magnetic stimulation of the left cerebellar hemisphere, i.e., contralateral to the side of auditory stimulation, as well as to be localized to left frontal electrode sites, i.e., homolateral to cerebellar stimulation. A fronto-central topography of the SSAER with greatest amplitude at contralateral frontal sites is a standard finding when EEG recording is performed with balanced earlobe reference electrodes (Azzena et al. 1995; Maiste et al. 1995; Pastor et al. 2002). Our finding of rTMS-effects to predominate after left cerebellar stimulation, contralateral to the stimulated ear, was not necessarily expected, given that monoaural auditory input does project bilaterally to both hemispheres. However, modulation of auditory evoked cortical responses through ipsilateral cerebellar control is in agreement with the findings from PET. These showed unilaterally predominating cerebellar coactivation, opposite to the stimulated ear, together with stronger activation of the primary and secondary auditory cortices homolateral to the cerebellar activation site (Pastor et al. 2002). In contrast to other cortical regions, the auditory cortex appears to send fibers mainly to cell groups projecting to the ipsilateral crus II (Brodal 1983). The projections from the auditory cortex to the cerebellum are by the secondary auditory area (AII) and the adjacent auditory association areas of the superior temporal gyrus (STG) and superior temporal plane (STP) to the dorsolateral, lateral, and peripeduncular pontine nuclei (Schmahmann and Pandya 1991). Therefore, if the auditory cortex follows the general principle of reciprocal interconnections with the cerebellum, namely if the cortical areas that project to the cerebellum by the pons are themselves the target of cerebellar output by the thalamus (Middleton and Strick 1998), magnetic stimulation of auditory areas of the cerebellar hemisphere would be expected to modify homolateral auditory cortex function. This may explain the great asymmetry of the rTMS effect over the hemisphere crus II areas, i.e., that rTMS over the left posterior fossa, targeting the auditory association area of the cerebellar hemisphere, modulates the SSAER over homo- but not contralateral cortex.

The baseline amplitude of the SSAER was similar at all explored auditory frequencies (32, 40, 47 Hz). Auditory steady-state responses recorded from the scalp in the awake and passive state show on average maximum amplitudes at approximately 40 Hz (Galambos et al. 1981), but individual variability has been observed (Stapells et al. 1984). We requested from the subjects to detect silently the changes of frequencies within each block of auditory stimulation. This attentional load may have modified the amplitude of the recorded SSAER in a way that equalized the responses at the three explored frequencies. Visually induced steady-state potentials are modulated by shifts of spatial attention (Belmonte 1998; Muller and Hillyard 2000). In the auditory modality, no effect of attention was found on the amplitude and phase of steady-state evoked potentials for stimulus rates between 37 and 41 Hz (Linden et al. 1987) but lower and higher rates have not been tested. It might thus be speculated that attentional modulation has a stronger impact on the 32- and 47-Hz SSAERs than on the 40-Hz response, latter showing already elevated amplitude values.

The modification of steady-state responses after 10 min of 1-Hz rTMS is most significant for auditory click-trains presented at 40 Hz, followed by 32 Hz and is consistent across individuals. Our findings of greater modulation of 40-Hz cortical responses and a fronto-central topography are consistent with a previous study on SSAERs, designed without attentional load and recorded with EEG and PET (Pastor et al. 2002). Also, the oscillatory responses induced by auditory stimulation at around 40 Hz typically have larger amplitudes than those evoked by other stimulation rates, which may imply stronger or more synchronous cerebello-cortical interactions at this frequency. In addition to endorsing that the cerebellum is playing a role in the generation of the 40-Hz SSAER, our results suggest that cerebellar implication might generalize to other frequencies in the lower gamma frequency band (30–40 Hz), although this has to be considered preliminary given that the TMS-effect on the 32-Hz SSAER did not reach significance. Yet, the present results demonstrate that the cerebellum is not involved in the control of oscillatory responses across the entire frequency range. All neuronal populations have "preferential" frequencies, and our results indicate that for cerebello-cortical interactions, cerebellar neurons preferentially resonate at specific frequencies in the gamma band. Further studies are needed to analyze a wider range of frequencies, but in the present study it is interesting to see selective effect of rTMS on SSAER fading at 47 Hz. Future studies using individual anatomical localization of the cerebellar area, via functional neuroimaging techniques, may also help to account for inter-individual differences regarding peak-frequency of maximum

SSAER amplitude and for the influence of attention onto the thalamo–cortical–cerebellar network.

Our results serve as a further example of physiologic effects of rTMS over the cerebellum. The main bulk of evidence on effects of cerebellar TMS comes from motor paradigms. However, because TMS over the posterior fossa causes a simultaneous stimulation of peripheral cutaneous and muscular afferents that influences the excitability of spinal circuits, parts of the effects of cerebellar TMS on motor tasks can be explained by spinal mechanisms rather than modulation of cortical circuitry (Gerschlager et al. 2002). The fact that rTMS over the cerebellar hemisphere led to topographically congruent, cerebral cortical changes in SSAER offers a way to study cerebellar modulation of cortical functions disentangled from the effects of other local inputs, i.e., originating in midbrain or peripheral structures. In our study, the differential modulation of cortical responses at 40 versus 47 Hz supports a cortical, not midbrain (i.e., cochlear nuclei) control.

In conclusion, modulation of the cerebellar output by rTMS modifies cortical oscillatory activity associated with an auditory task, namely the steady-state auditory response to click-trains. Our findings add novel information about the functional role of the cerebellum in non-motor tasks. Overall, our results demonstrate that rTMS applied during specific sensory or cognitive tasks and coupled with concurrent EEG recording is a valuable tool to explore cerebro-cerebellar functional connectivity.

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