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RESEARCH ARTICLE

Repetitive TMS of cerebellum interferes with millisecond time processing

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Abstract Time processing is important in several cognitive and motor functions, but it is still unclear how the human brain perceives time intervals of different durations. Processing of time in millisecond and second intervals may depend on different neural networks and there is now considerable evidence to suggest that these intervals are possibly measured by independent brain mechanisms. Using repetitive transcranial magnetic stimulation (rTMS), we determined that the cerebellum is essential in explicit temporal processing of millisecond time intervals. In the first experiment, subjects' performance in a time reproduction task of short (400–600 ms) and long (1,600–2,400 ms) intervals, were evaluated immediately after application of inhibitory rTMS trains over the left and right lateral cerebellum (Cb) and the right dorsolateral prefrontal cortex (DLPFC). We found that rTMS over the lateral cerebellum impaired time perception in the short interval (millisecond range) only; for the second range intervals, impaired timing was found selectively for stimulation of the right DLPFC. In the second experiment, we observed that cerebellar involvement in millisecond time processing was evident when the time intervals were encoded but not when they were retrieved from memory. Our results are consistent with the hypothesis that the cerebellum can be considered as an internal timing system, deputed to assess millisecond time intervals.

Keywords Time perception · Timing · Transcranial magnetic stimulation · rTMS · Cerebellum

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Introduction

The accurate perception of the passage of time is crucial to execute actions in everyday life. Based on the relevant timescales and the presumed underlying neural mechanisms, temporal processing has been categorized into four different time scales: microseconds, milliseconds, seconds, and circadian rhythms (Mauk and Buonomano 2004). Interval timing in the second to minutes range is crucial in decision-making, while millisecond timing is required for motor control, speech, playing music and dancing (Buhusi and Meck 2005). Temporal processing of millisecond and second time intervals may depend on different neural networks (Gibbon et al. 1997; Ivry and Spencer 2004) and there is considerable evidence suggesting that they are possibly measured by independent brain mechanisms (Lewis and Miall 2003a). In animal models, the cerebellum seems not essential for interval timing while it is required for accurate millisecond timing (Koekkoek et al. 2003; Buhusi and Meck 2005).

In humans, the role of cerebellum in timing is still debated, since it has not been clearly established

whether the cerebellum is specifically engaged for time processing in the range of milliseconds. Poor acuity on a time discrimination task in the ranges of milliseconds and seconds has been reported in patients with lesions of the cerebellum (Ivry et al. 1988; Nichelli et al. 1996; Mangels et al. 1998). In their study, Malapani et al. (1998), using a peak interval procedure, reported that variability of time estimates in the second range increased in patients with focal lesion of the lateral cerebellum (cortex and nuclei), compared with patients with lesions of the mesial cerebellum and vermis. Mangels et al. (1998) found that patients with neocerebellar damage showed impairments in discriminating intervals in the millisecond range as well in the second range. However, a recent investigation by Harrington et al. (2004), failed to detect clear time processing abnormalities in patients with cerebellar strokes. Subtle deficits in time reproduction, but not in time perception, were observed in patients with medial and lateral damage involving the middle and superior cerebellar lobules, and the results were interpreted as not supporting a role for the cerebellum in time keeping operations.

Furthermore, neuroimaging studies showed disparate results, since this structure appeared to be activated by timing intervals in both millisecond and second ranges (Jeuptner et al. 1995; Penhune et al. 1998; Coull and Nobre 1998; Schubotz et al. 2000; Rao et al. 2001; Lewis and Miall 2003a; Macar et al. 2006; Smith et al. 2003). Recently, greater activity was observed in the left cerebellar hemisphere and the frontal operculum during measurement of sub-second (0.6 s) intervals in comparison with supra-second (3 s) intervals, suggesting that distinct brain networks could be used for the two durations (Lewis and Miall 2003b). Although the cerebellum is crucial for timing functions, other studies have shown that time estimation processes seem to depend on a right hemispheric cortical network involving the basal ganglia and different cortical areas (Harrington et al. 1998; Koch et al. 2002, 2003, 2004; Pouthas et al. 2000; Smith et al. 2003). Neuropsychological work (Harrington et al. 1998; Koch et al. 2002), TMS investigations (Koch et al. 2003, 2004; Jones et al. 2004) and neuroimaging studies (see Lewis and Miall 2003b for reviews) indicated that the DLPFC is another crucial region supporting timing functions, especially subserving time intervals in the range of seconds.

Thus, although the lateral cerebellum is relevant in timing processes, it has yet to be defined if its activity supports timing of different range intervals. The aim of the current study was to investigate whether a virtual lesion of the lateral cerebellum or the right DLPFC would produce selective impairment in processing of millisecond or second time range. Therefore, we used repetitive transcranial magnetic stimulation (rTMS) to analyse, in a sample of normal subjects, the involvement of these sites in a time reproduction task with different time ranges. In the first experiment, rTMS was applied to the left lateral cerebellum (lCb), right lateral cerebellum (rCb) and the right DLPFC, prior to execution of the task. A 1 Hz frequency rTMS paradigm, shown to induce an inhibition of the stimulated cortical area lasting beyond the duration of the train (Chen et al. 1997; Oliveri et al. 2005) was used. In the second experiment, high-frequency rTMS trains at 20 Hz were delivered over the left and right lateral cerebellum during the different phases of the task (encoding or reproduction) to transiently interfere with the stimulated cortical area during a specific phase of the task.

Materials and methods

Subjects

Seventeen normal volunteers with normal or corrected vision participated in this study (nine females, eight males; 22–35 years old). Nine subjects participated in the first experiment and eight in the second. All subjects gave their informed consent and the local ethics committee's approval was obtained. The experiments were performed according to the Declaration of Helsinki. All subjects were right-handed according to the Edinburgh handedness test (Oldfield 1971).

Experimental procedure

We used a time reproduction task that consists of an encoding phase in which the temporal interval is perceived and by a reproduction phase in which subjects explicitly retrieve from memory the previously encoded interval. The task is similar to that used by Jones et al. (2004).

Subjects were seated opposite a computer screen with a response button placed at a distance of 60 cm in front of them. Initially, the task was described to the subjects and they were then given five practice trials to ensure that they fully understood it. The task involved reproducing an interval of time that was presented visually to the subjects. At the start of each trial a blue circle (diameter 20 mm) was presented in the centre of a grey screen and after a specified period disappeared. The subjects were instructed to estimate the duration for which the blue circle was visible (encoding phase). Immediately after the encoding phase, a red circle of the same size was presented at the centre of the screen.

The subjects were asked to recall the time interval that they had just estimated (reproduction phase). When they considered that the same amount of time had elapsed, then they were to press the response button and the red circle disappeared. No feedback was given. All subjects used their right index finger to respond.

For each rTMS site, a complete run consisted of 50 trials in which the subjects estimated intervals in the range of milliseconds and 50 trials in which the subjects estimated intervals in the range of seconds. Millisecond trials had a standard interval of 400, 450, 500, 550 or 600 ms (average 500 ms). Supra-second trials had a standard interval of 1,600, 1,800, 2,000, 2,200 or 2,400 ms (average 2,000 ms). The computer programme selected interval lengths pseudo-randomly, such that, each subject received ten presentations of each interval length within the 50 trial block. The inter-trial intervals were one of five randomly selected lengths (500, 600, 700, 800 and 900 ms). The different interval lengths were used to prevent learning.

Experiment 1

In the first experiment, rTMS was applied at 1 Hz frequency for 10 min (corresponding to 600 stimuli), at an intensity of 90% of the resting motor threshold (RMT). RMT was defined as the lowest TMS intensity (as assessed with single-pulse TMS on the contralateral motor cortex) able to induce a visible muscle twitch of the contralateral hand (i.e. ipsilateral to cerebellar stimulation) in at least 50% of a sequence of ten consecutive trials. rTMS was applied over the left and right lateral Cb and over the right DLPFC. This procedure is known to induce an inhibition of the stimulated cortical area lasting beyond the duration of the train (Chen et al. 1997; Oliveri et al. 2005). Right DLPFC was selected on the basis of previous TMS studies showing that stimulation of this cortical area may induce abnormal time processing in the range of seconds (Jones et al. 2004; Koch et al. 2003). rTMS sessions were performed on different days, one for each site. First, a baseline condition was included in which subjects completed two 50 trials blocks (one in the range of millisecond, one in the range of seconds) before rTMS was delivered. In each session, the task was then performed immediately after the cessation of the rTMS train.

Experiment 2

In a second phase of the study rTMS trains of four stimuli at 20 Hz frequency (stimulation time: 150 ms) were delivered at an intensity of 90% of motor threshold over the left lCb, right lateral cerebellum and to a control scalp site on the vertex (Cz of the 10–20 EEG system). This procedure is known to transiently interfere with the stimulated cortical area. Filled intervals are usually perceived longer than unfilled intervals. Since the sound of TMS click may contribute in generating a similar effect, and for the reasons mentioned earlier, we performed also a control experiment applying rTMS over a control site (Cz). The experiments were performed on different days. Using the same target intervals as in experiment 1, subjects estimated time intervals in the range of milliseconds and in the range of seconds. In each session four blocks were performed, in which rTMS was applied either at the beginning of the encoding or the reproduction phases over the left or right lateral cerebellum (main experiment) or over the vertex (control experiment). A baseline condition was done prior to each session, in which subjects completed two 50 trial bocks without rTMS occurring. The inter-trial intervals were one of five randomly selected lengths (4,000, 4,500, 5,000, 5,500 and 6,000 ms). Longer ITIs were used in experiment 2, since rTMS was applied "on-line". For both experiments we used a balanced-order block design. The order of presentation of the sites of stimulation was counterbalanced between subjects. Furthermore, in every session, the order of presentation of the blocks (millisecond/second ranges) was counterbalanced between subjects.

rTMS protocol

A MagStim Rapid magnetic stimulator (Magstim, Whitland, UK), connected with a figure-of-eight coil with a diameter of 70 mm was used to deliver rTMS over the scalp sites corresponding to the left and right lateral Cb, and right DLPFC.

rTMS over the lateral (left or right) cerebellum was applied using the same scalp co-ordinates as Theoret et al. (2001) (1 cm under and 3 cm left/right to the inion). The coil was positioned tangentially to the scalp, with the handle pointing superiorly. The current in the coil was directed upward, which induced downward current in the cerebellar cortex. This coil position was found to be optimal for suppressing the contralateral motor cortex in single pulse TMS investigations (Ugawa et al. 1995; Hashimoto and Ohtsuka 1995; Daskalakis et al. 2004) and to interfere with procedural learning when a 1 Hz rTMS paradigm was adopted (Torriero et al. 2004).

For the DLPFC, the point of intersection of the coil loops was lined up with the F3 (left) and F4 (right) site, at the level of the gyrus frontalis secundus and of the

caudal portion of sulcus frontalis medius (i.e. DLPFC: BA9/46) according to the guidelines of previous studies (Pascual-Leone and Hallett 1994; Oliveri et al. 2001). For rTMS of the DLPFC, the coils were held tangentially to the scalp, with the handle pointing posteriorly so as to induce a current flowing parallel to the sagittal axis with a posterior to anterior direction. Precise anatomical information about the brain area stimulated was obtained by performing an MRI on a single experimental subject after marking the cerebellar and frontal scalp sites with capsules containing soy oil. A T1-weighted image was produced with a Siemens 1.5 T Vision Magnetom MR system (Erlangen, Germany; MPRAGE sequence, 1 mm isotropic voxels). A line parallel to the capsule and tangential to the surface of the skull, representing the coil orientation, and a perpendicular line originating in the centre of the capsule, representing the centre of the area where the induced magnetic field was maximum, were drawn on sagittal, coronal and horizontal planes (Fig. 1).

Data analysis

Reproduced times were the dependent variable used to measure performance. Data were analysed for accuracy and precision of subjective time estimates, indexed by average of the mean estimations (accuracy) and coefficient of variation (variability; CV = semi-interquartile range/median).

In the first experiment, different ANOVAs for repeated measures with condition (pre-rTMS vs. post-rTMS), site (left Cb vs. right Cb vs. right DLPFC) and duration (milliseconds vs. seconds) main effects were applied on accuracy and variability. In experiment 2, different ANOVAs for repeated measures with condition (baseline, encoding rTMS, reproduction rTMS), site (left Cb, right Cb and Cz) and duration (milliseconds vs. seconds) main effects were applied on accuracy and variability.

Mauchley's test examined for sphericity. A p value <0.05 was considered significant. A significant main effect in the ANOVA was followed by Duncan's post hoc analysis. The Greenhouse–Geisser correction was used for non-spherical data.

Results

In the first experiment, subjects' performances in a time reproduction task in the millisecond (400–600 ms)

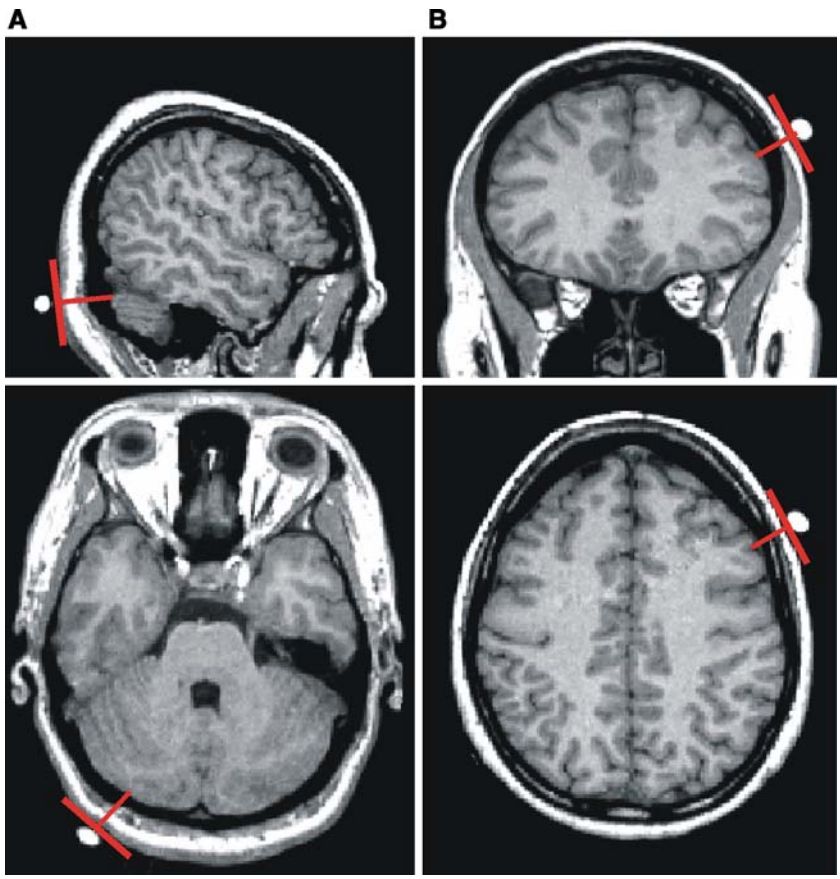

Fig. 1 Precise anatomical information about the brain area stimulated was obtained by performing a T1-weighted image MRI on a sample subject after marking the cerebellar (**a**) and frontal (**b**) scalp sites with capsules containing soy oil. A line parallel to the capsule and tangential to the surface of the skull, representing the coil orientation, and a perpendicular line originating in the center of the capsule, representing the center of the area where the induced magnetic field was maximum, were drawn on sagittal, coronal and horizontal planes

and second (1,600–2,400 ms) intervals were evaluated immediately after application of inhibitory off-line 1 Hz rTMS trains over the left and right lateral cerebellum and the right dorsolateral prefrontal cortex (DLPFC). For accurate data, there was a significant ANOVA-three-way interaction (duration main effect: $F_{(1,8)} = 1{,}435$, $p < 0.00001$; site × condition × duration: $F_{(1,8)} = 7.41$; $p < 0.01$). Left cerebellar stimulation in comparison with basal condition, induced an overestimation of the millisecond intervals (546 ms vs. 601 ms; $p < 0.02$ at post hoc analysis), while did not interfere with second range duration (1,933 ms vs.1,879 ms; $p = 0.09$). Right cerebellar rTMS did not alter either millisecond (566 ms vs. 571 ms; n.s.) or second duration (1,941 ms vs. 1,928 ms; n.s.). Finally, right DLPFC stimulation did not modify the reproduction of millisecond intervals (579 ms vs. 581 ms; n.s.) while it induced an overestimation of the second interval (1,867 ms vs. 1,975 ms; $p < 0.05$ at post hoc analysis) (Fig. 2).

Variability was not altered by rTMS, since the ANOVA applied on CVs with condition (pre-rTMS vs. post-rTMS), site (left Cb vs. right Cb vs. right DLPFC) and duration (millisecond vs. second), did not show any significant effect (Table 1).

In experiment 2, for accurate data, there was no significant interaction shown by a three-way ANOVA (site × condition × duration: $F_{(1,8)} = 0.5$; p = n.s.). On the basis of the results obtained in experiment 1, suggesting a specific role of lateral CB in millisecond time processing, we performed subsequent ANOVAs on subjects' performances in the millisecond range for each site of stimulation. There were significant main effect of condition for left Cb rTMS (condition main factor: $F_{(1,7)} = 9.47$, $p < 0.001$; encoding vs. baseline $p < 0.005$ and encoding vs. reproduction $p < 0.001$ at post

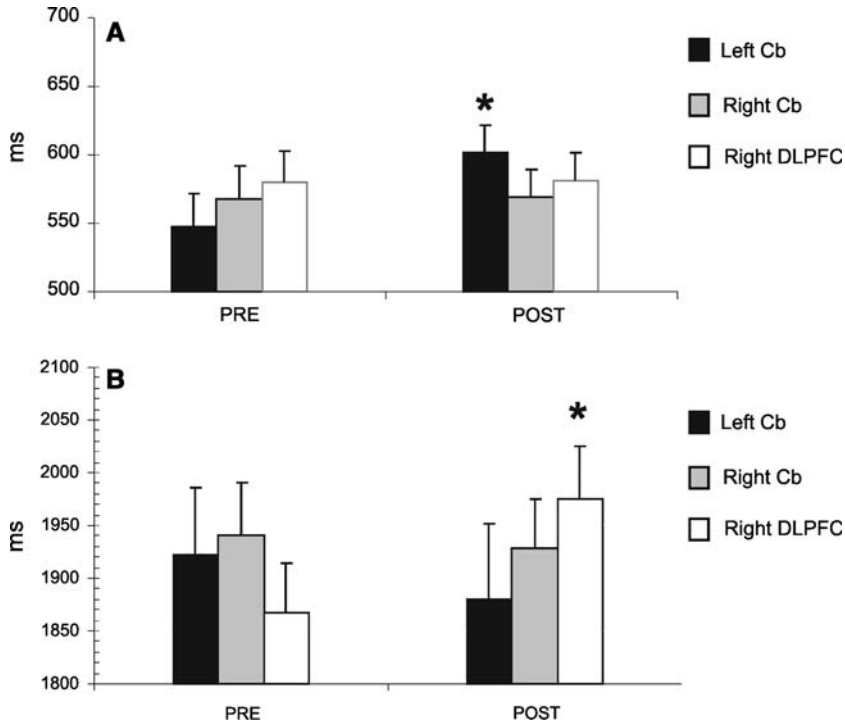

Fig. 2 Different rTMS effect on time perception depending on the site of stimulation and the duration of time intervals. **a** During the reproduction of millisecond time intervals rTMS induced an overestimation of mean estimation only when applied over the left lateral cerebellum. **b** For the second time intervals accuracy was affected only for right DLPFC stimulation. *Black bars* left cerebellum; *grey bars* right cerebellum; *white bars* right DLPFC. *Error bars* indicate 1 standard error of mean. $^{*}p < 0.05$

Table 1 Mean (±SD) of accuracy and coefficient of variation before and after rTMS for millisecond range and second range duration

	Accuracy (ms)		CVs	
	Pre	Post	Pre	Post
Millisecond range				
Left Cb	546.4 ± 71	601.3 ± 61	0.23 ± 0.06	0.24 ± 0.06
Right Cb	566.1 ± 64	571 ± 74	0.20 ± 0.03	0.22 ± 0.05
Right DLPFC	579 ± 59	581 ± 69	0.26 ± 0.04	0.27 ± 0.08
Second range				
Left Cb	1933.2 ± 190	1879.1 ± 215	0.22 ± 0.03	0.23 ± 0.02
Right Cb	1940.7 ± 150	1928.4 ± 139	0.19 ± 0.02	0.21 ± 0.05
Right DLPFC	1867.3 ± 90	1974.8 ± 103	0.25 ± 0.09	0.24 ± 0.08

hoc analysis) and right Cb rTMS (condition main factor: $F_{(1,7)} = 6.19$, $p < 0.01$; encoding vs. baseline $p < 0.01$ and encoding vs. reproduction $p < 0.01$ at post hoc analysis) showing that overestimation occurred selectively when rTMS was applied during the encoding phase (Fig. 3). No effect was found for Cz stimulation. The CVs analysis did not show any significant effect when rTMS was applied during the encoding or the reproduction phase, revealing that variability was not altered by rTMS.

Discussion

Our findings reveal that the cerebellum is essential for the explicit timing of intervals in the millisecond but not in the second range, and it is specifically engaged during the encoding processes. Although both hemispheres contribute to timing, the role of the left lateral cerebellum seems prominent. On the other hand, we found that the right DLPFC is critically involved in supra-second time intervals processing, while the cerebellum does not seem to be implicated. Taken together, these results support the existence of a cerebellar-prefrontal network for conscious time perception with a clear dissociation between the millisecond and second time processing.

Disturbances in temporal estimates have been associated with medial and/or lateral damage to the middle- to superior-cerebellar lobules, rather than simply to the lateral cerebellar hemispheres (Ivry et al. 1988; Harrington et al. 2004). These findings are in keeping with most functional imaging studies in healthy adults, which show that more superior cerebellar lobules, including the anterior lobe (IV and V), are activated during motor timing tasks (Jeuptner et al. 1995; Schubotz et al. 2000; Smith et al. 2003). An important limitation of our study is that we did not use a neuro-navigation system that permits high spatial resolution. However, previous investigations demonstrated that cerebellar TMS predominantly affects the posterior and superior lobules (Ugawa et al. 1995; Hashimoto and Othsuka 1995). In previous studies, cerebellar TMS was able to interfere with visually guided saccades (Hashimoto and Othsuka 1995), smooth pursuit eye movements (Othsuka and Enoki 1998), paced finger tapping (Theoret et al. 2001), coordinated eye and head movements (Nagel and Zangemeister 2003) and procedural learning (Torriero et al. 2004). The mechanism of action of

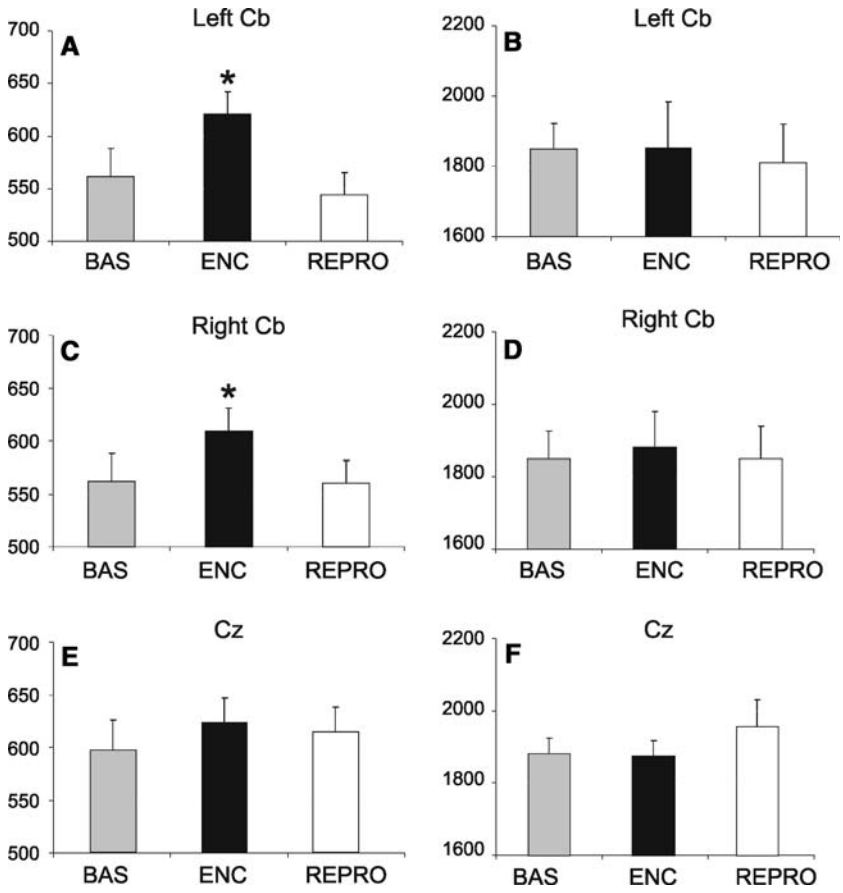

Fig. 3 The specific contribution of the lateral cerebellum during the different processes of encoding and reproduction of time intervals was investigated in a second series of experiments using a different on-line rTMS paradigm. rTMS altered millisecond timing selectively during the encoding phase when delivered over both the left (**a**) and right lateral Cb (**c**). No significant modification was found when rTMS was applied on left and right Cb for second time intervals, in both encoding and reproduction phases (**b** and **d**). No effect was observed when rTMS was delivered over a control site for both millisecond and second time (**e** and **f**). *X*-axis: *BAS* basal, *ENC* encoding phase, *REPRO* reproduction phase. *Y* values are expressed in ms. *Error bars* indicate 1 standard error of mean. $^{*}p < 0.05$

cerebellar TMS acts has been proposed to directly interfere with the activity of the inhibitory Purkinje cells, thus reducing the drive from the dentate and interposite nuclei to the cortex via the thalamus (Daskalakis et al. 2004).

Additionally, Purkinje cells are activated during acquisition and coding of learned timing (Kotani et al. 2003) and long-term depression (LTD) of these cells is necessary for learning-dependent timing of Pavlonian-conditioned eyeblink responses in the range of milliseconds (Koekkoek et al. 2003). On the basis of this, we propose that cerebellar rTMS alters time perception through transient inhibition of the Purkinje cells of the posterior and superior lobules of the lateral cerebellum, and reveals that these neurons are directly involved in tracking the passage of millisecond time. Although debated, LTD of motor cortex neurons by 1 Hz rTMS is plausible and has been invoked as an explanation in previous reports. Converging evidence supports the idea that the nature of the rTMS-induced inhibition is LTD-like (Chen et al. 1997). Thus 1 Hz cerebellar rTMS could have interfered with the physiological LTD activity of the Purkinje cells, which is supposed to be necessary for timing mechanisms in the millisecond range.

Our results are supported by a recent review of neuroimaging studies, examining time measurement showing that most of the 17 papers, which involved measurement of millisecond intervals, report activity in the cerebellum, while four of the seven which scanned the cerebellum and examined only intervals longer than 1 s reported activity there (Lewis and Miall 2003b). The authors proposed that the lateral cerebellar circuits are also involved in timing processes sustaining an explicit representation of time (Lewis and Miall 2003b). Consistent with this view, the task adopted in our study requires an explicit timing representation as well. Furthermore, the finding that especially the left posterior cerebellum contributes to timing is in agreement with previous observations (Schubotz et al. 2000; Smith et al. 2003).

Finally, the right DLPFC may constitute the neural structure where time in the second range is represented and stored. Our results are in agreement with previous fMRI investigations reporting constant prefrontal activation during measurement of intervals in the second range (Rao et al. 2001; Nenadic et al. 2003), with lesion studies (Mangels et al. 1998; Mimura et al. 2000; Koch et al. 2002) and TMS studies (Koch et al. 2003, 2004; Jones et al. 2004).

For interval timing in the range of seconds, theoretical models hypothesize distinct stages of processing in a hierarchical order based on the existence of an oscillating pacemaker, which constitutes an internal clock (Gibbon et al. 1997) or dispense with the pacemaker entirely and propose that time may be measured using the decaying strength of memory traces (Staddon and Higa 1999). Studies in animals suggest that a specific basal ganglia-prefrontal circuit, involving particularly the dopaminergic output of the substantia nigra (SNc) to the striatum, could be responsible for time intervals processing in the range of seconds (Meck and Benson 2002; Hinton and Meck 2004). However, it remains unclear if the basal ganglia are involved in timing in the range of hundreds of milliseconds (Ivry and Keele 1988; Spencer and Ivry 2003) Alternatively, it has been proposed that the basal ganglia are an integral part of decision processes concerning time processing (Ivry and Spencer 2004b), while the cerebellum provides representation of the precise timing salient events in the millisecond range, determining the onset and offset of movements or the duration of a stimulus (Ivry et al. 2002; Spencer et al 2003). According to this model, we could speculate that the overestimation of time intervals in the millisecond range following rTMS of the cerebellum may reflect a slowing in the cerebellar event timing system.

The Lewis and Miall (2003b) model argued that an "automatic" timing system is primarily involved in the continuous timing of millisecond-range intervals that are defined by movements, while a "cognitively" controlled timing system is preferentially involved in the measurement of discrete seconds-range intervals. Although in our study we did not use a task directly requiring automatic motor operations, even if target intervals were continuous and not discrete, in the two duration tasks subjects may get into a different "cognitive set"; in the millisecond condition the task would be performed more automatically and then rely on cerebellar structures and not engage frontal regions; on the other hand, in the longer interval condition, the task would require increased cognitive demands and the right DLPFC could be more engaged, rather than the cerebellum. Therefore, another possibility is that, the dissimilar contribution of cerebellum and DLPFC for millisecond and seconds range processing may depend also on different cognitive demands in the different tasks and not only on the duration of time intervals.

In conclusion, although a clear dissociation between the cerebellar and other cortical and sub-cortical structures' contributions to temporal processing of different duration remains elusive, our results suggest that the cerebellum might represent a specialized timing system supporting encoding of intervals spanning hundreds of milliseconds.

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