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Time-course of "off-line" prefrontal rTMS effects — a PET study ☆

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Low-frequency "off-line" repetitive transcranial magnetic stimulation (rTMS) over the course of several minutes has attained considerable attention as a research tool in cognitive neuroscience due to its ability to induce functional disruptions of brain areas. This disruptive rTMS effect is highly valuable for revealing a causal relationship between brain and behavior. However, its influence on remote interconnected areas and, more importantly, the duration of the induced neurophysiological effects, remain unknown. These aspects are critical for a study design in the context of cognitive neuroscience.

In order to investigate these issues, 12 healthy male subjects underwent 8 $H_2^{15}O$ positron emission tomography (PET) scans after application of long-train low-frequency rTMS to the right dorsolateral prefrontal cortex (DLPFC). Immediately after the stimulation train, regional cerebral blood flow (rCBF) increases were present under the stimulation site as well as in other prefrontal cortical areas, including the ventrolateral prefrontal cortex (VLPFC) ipsilateral to the stimulation site. The mean increases in rCBF returned to baseline within 9 min. The duration of this unilateral prefrontal rTMS effect on rCBF is of particular interest to those who aim to influence behavior in cognitive paradigms that use an "off-line" approach.

Keywords: After effects; Cerebral blood flow; Low frequency; Prefrontal cortex; Transcranial magnetic stimulation

Introduction

TMS has become an indispensable investigation tool in cognitive neuroscience. Its ability to transiently disrupt normal function of human brain regions makes it a unique tool for studying the causal contribution of different brain areas to behavior. A very promising approach is the application of low-frequency repetitive TMS (rTMS) for several minutes before performing a given task in order to partially elude the unspecific effects of concurrent rTMS stimulation (Abler et al., 2005; Pascual-Leone et al., 1998; Robertson et al., 2003). This approach, also referred to as "off-line" rTMS, has been used extensively in recent years. It has been applied, inter alia, to study parietal contributions to spatial attention (Hilgetag et al., 2001) and spatial hearing (Lewald et al., 2002), or prefrontal contributions to visual working memory (Mottaghy et al., 2002), affective processes (d'Alfonso et al., 2000) and decision making (Knoch et al., 2006a,b).

Despite considerable advances in this field of research, cognitive neurosciences still rely primarily on the use of functional imaging. Imaging experiments, however, do not allow drawing firm conclusions about the nature of neural network nodes: activation could be spuriously correlated with task performance and not necessary for proper task execution (Sack et al., 2005, 2007; Sack and Linden, 2003; Walsh and Cowey, 2000). rTMS seems to be a method well suited for studying the functional relevance of a cortical region, which has been previously identified by a functional imaging experiment, for a specific cognitive function (Hallett, 2007).

When designing an experiment using "off-line" low-frequency rTMS, several aspects should be considered. First, the *duration* of the "off-line" disruptive effect restricts the number of trials in an experiment and, hence, the data collection. Previous studies (d'Alfonso et al., 2000; Mottaghy et al., 2002; Robertson et al., 2001) have provided some information about the duration of behavioral effects after low-frequency "off-line" long-train rTMS applied to the dorsolateral prefrontal cortex (DLPFC). The findings of these studies led to the formulation of a rule of thumb: the duration of the after effects is generally half the duration of the stimulation train (Robertson et al., 2003). However, these studies only report behavioral measures and provide no information about the duration of the neurophysiological effect of "off-line" low-frequency rTMS applied to the prefrontal cortex. Second, stimulation of the homologue contralateral region as a *control stimulation site* has proven to be an expedient

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strategy for the control of the side effects of rTMS intervention. Likewise, the side effects of rTMS intervention that ultimately influence the outcome variable are similar. rTMS induces muscle-twitches and tickling sensations at the stimulation site. Especially when rTMS is applied to frontal regions, it causes discomfort, constituting a possible confounding effect (Abler et al., 2005). As these side effects typically are equally present when stimulating the homologue contralateral region one can control for these side effects by also stimulating this region. However, a *contralateral* control stimulation is only reasonable if a unilateral stimulation leads to unilateral, and not bilateral neurophysiological "off-line" effects. It is therefore important to know whether "off-line" rTMS leads to unilateral or bilateral lasting effects. Third, related to the second point, one should consider that applying rTMS to a given brain region not only affects the target site itself, but also brain areas effectively connected to the target area. Such *remote effects* evoked by low-frequency rTMS over prefrontal areas have been shown in several studies (Kimbrell et al., 2002; Knoch et al., 2006c; Nahas et al., 2001; Ohnishi et al., 2004; Speer et al., 2003). These studies, however, differed from the usual "off-line" protocol in that either regional cerebral blood flow (rCBF) (Nahas et al., 2001; Speer et al., 2003) or glucose uptake (Kimbrell et al., 2002) was measured "on-line" (i.e., during rTMS application), or in that the duration of the stimulation trains were shorter than usual in the "off-line" approach (Knoch et al., 2006c; Ohnishi et al., 2004).

Despite the wide-spread use of "off-line" rTMS in cognitive tasks, and more recently, social cognitive neuroscience, no experiment has ever investigated the time-course of the neurophysiological lasting effects after a single train of low-frequency rTMS applied to the prefrontal cortex. We specifically designed our study to assess the issues mentioned above. We were particularly interested in the after effects of right sided prefrontal stimulation as we previously found lateralized behavioral effects using this stimulation protocol (Knoch et al., 2006a,b). We used $H_2^{15}O$ PET to assess the effects of rTMS on regional cerebral blood flow. An advantage of this imaging technique is the possibility to compare the relative size of regional blood flow across different brain regions and over time. We applied one single train of low-frequency rTMS to the right DLPFC of 12 subjects and subsequently performed 8 sequential $H_2^{15}O$ PET scans.

Materials and methods

Subjects

12 healthy right-handed male subjects (mean age 25.3 years, SD 4.0 years) participated in the study that the local ethics committee approved. All subjects provided written informed consent. Subjects had no history of psychiatric illness or neurological disorder and were naive to TMS.

PET procedures

We used $H_2^{15}O$ PET as a measure of regional synaptic activity. Eight sequential scans were performed in each subject (1 baseline scan, 7 post stimulation scans). PET scans were acquired on a whole-body scanner (DLS GE Medical Systems, Waukesha, WI, USA) in 3D mode with a 15-cm axial field of view. In each scan, 300–400 MBq $H_2^{15}O$ was administered as a bolus using a remotely controlled injection device. Injection of the $H_2^{15}O$ bolus was initiated with an automatic preparation and pump system 30 s before the start of the actual $H_2^{15}O$ PET scan. The accumulated radioactivity counts over 60 s were then taken as measure for cerebral blood flow. Data were reconstructed into 35 image planes with a resolution of 7 mm full-width at half-maximum (FWHM). Subject preparation included the insertion of an indwelling cubital vein catheter for injection of the $H_2^{15}O$. In order to ensure complete head fixation, the head of the subject was confined in a vacuum cushion. The scan room was darkened and subjects wore foam earplugs for hearing protection. One low-dose CT scan for attenuation correction was performed at the beginning of the experiment, immediately followed by the baseline $H_2^{15}O$ scan. Subjects kept their eyes closed during all scans. The remaining seven scans were divided into two blocks. Each block consisted of three and four scans, respectively (see Fig. 1). The order of the two blocks was pseudorandomized across subjects.

Location of the target region

For the exact localization of the stimulation site, a T1-weighted MRI was acquired for all subjects prior to the PET-experiment. The right DLPFC was located based on fixed coordinates: $x=39$, $y=37$, $z=22$; radius=6 in Talairach space. These coordinates were then transformed to each subject's native brain space using Brainvoyager QX 1.6 software (Brain Innovation BV, Maastricht, NL). The real-time neuronavigation option for Brainvoyager QX 1.6 with the Zebris CMS20S measuring system for real-time motion analysis (Zebris Medical GmbH, Isny, DE) allowed correct placement of the TMS coil in space.

rTMS procedure

rTMS was applied to the right DLPFC for 15 min before each PET scanning block (see Fig. 1). A Magstim Rapid 2 Stimulator (Magstim, Winchester, USA) and a commercially available figure-of-eight-coil (70 mm diameter double circle, air-cooled) was used. Intensity of stimulation was set to 54% of maximum stimulator output. The coil was held tangentially to the subject's head with the handle pointing rostrally. Each subject received one train of 15 min duration at 1 Hz (900 pulses) before each block of PET scanning, amounting to a total of 1800 pulses per session and subject. The time interval between the two stimulation blocks was 30 min. The rTMS parameters employed were well within recommended safety guidelines (Wassermann et al., 1998).

Image analysis

All images were processed using Statistical Parametric Mapping software SPM99 (Wellcome Department of Imaging Neuroscience, UCL, UK; http://www.fil.ion.ucl.uk/spm). Image processing was

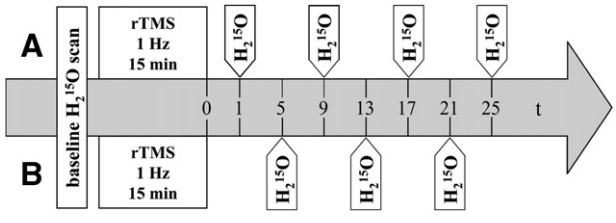

Fig. 1. Experimental design. To achieve a virtual time resolution of 4 min between $H_2^{15}O$ scans, we set up an interleaved scanning procedure. In every session, each scanning sequence was preceded by a baseline scan, which was followed by 15 min of 1 Hz rTMS at a fixed intensity of 54% of maximal stimulator output and either scanning block A or B. Time points (in min after rTMS train) of $H_2^{15}O$ scans are indicated within the grey arrow. *t*, time.

Table 1
Prefrontal brain regions that show significantly increased rCBF 1 min after rTMS

Brain region	BA	Hemisphere	MNI coordinates			T value
			x	y	z	
Dorsolateral prefrontal cortex [a]	45/46	R	50	48	16	5.31
Ventrolateral prefrontal cortex [b]	47	R	42	42	-8	4.39
Inferior frontal sulcus [b]	46/48	R	32	36	20	3.77

BA, Brodmann area; R, right.
[a] Maxima of regional increases in normalized rCBF based on the contrast "1 min>baseline" ($p<0.05$, corrected for multiple comparisons over the whole brain).
[b] Maxima of regional increases in normalized rCBF based on the contrast "1 min>baseline" ($p<0.001$, uncorrected).

performed as follows: head movements were corrected using the least-squares method and images were then normalized into stereotaxic space [Montreal Neurological Institute coordinates (MNI) as provided by SPM99] by bilinear interpolation using a PET template [SPM, 1999 (Friston et al., 1995)]. Scans were smoothed using a Gaussian filter of 15 mm in-plane and axial FWHM in order to improve the signal to noise ratio. To remove the effect of global differences in cerebral blood flow between scans, a subject-specific ANCOVA scaling of global activity to a mean of 50 ml/100 g/min was applied.

Region of interest analysis

We performed whole-brain analyses after 1, 5, 9, 13, 17, 21 and 25 min to determine the contrast with the largest rCBF response to low-frequency rTMS. Based on these analyses, the contrast "1 min>baseline" was used to determine regions of interest (ROIs) in the prefrontal cortex (see Table 1; for rCBF increases or decreases in other than prefrontal cortical regions please see Supplementary data). Analysis of later time points did not reveal additional clusters of either significantly increased or decreased rCBF. The ROIs were defined as follows: for the stimulation site, a spheric ROI was defined (MNI coordinates, radius and volume of ROI: $x=50$, $y=48$, $z=16$; radius=7 mm, volume=339 mm^3). A second spheric ROI was created in the right ventrolateral prefrontal cortex (VLPFC; $x=42$, $y=42$, $z=-8$; radius=7 mm, volume=339 mm^3) and a third spheric ROI was created in the right inferior frontal sulcus ($x=32$, $y=36$, $z=20$; radius=7 mm, volume=339 mm^3). Three homotopic contralateral ROIs were defined by mirroring the ROIs in the right hemisphere using MARSBAR (Brett et al., 2002). In order to control for unspecific arousal effects (Critchley et al., 2000, please see Discussion section), two additional control regions were defined in the cerebellum (ipsilaterally: $x=32$, $y=-70$, $z=-41$ and contralaterally: $x=-32$, $y=-70$, $z=-41$; both 16936 mm^3). ROIs were then normalized to baseline and analyzed using SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA). A two-way repeated measures ANOVA was calculated for each region with the factors: "hemisphere" (left/right) and "time" (1, 5, 9, 13, 17, 21 and 25 min).

Masked correlation analysis

Subject-specific time-courses were derived from the right DLPFC and the control region (left/right cerebellum) using MARSBAR (Brett et al., 2002). These individual time-courses were then incorporated as covariates of interest (correlation analysis). The linear association between rCBF at every time point and each value derived from the ROI in the right DLPFC and the control region was tested on a voxel-by-voxel basis using the SPM covariates option. To focus only on those regions within the prefrontal cortex that showed significant rCBF changes in response to "off-line" low-frequency rTMS, the correlation analysis of rCBF in the right DLPFC was subsequently masked by the subtraction contrast "1 min>baseline" ($p<0.001$, corresponding to a single-voxel threshold of $t>3.22$). Threshold in the correlation analysis was set at $p<0.001$, corresponding to a single-voxel threshold of $t>3.22$.

Results

Time-course of "off-line" prefrontal rTMS effects on rCBF

The contrast "1 min>baseline" revealed a significant rCBF increase at the stimulation site ($p<0.05$, corrected for multiple comparisons over the whole brain). Fig. 2 illustrates the anatomical coordinates of the stimulation site chosen for navigation and the corresponding region of increased rCBF. The contrasts at other time points (i.e. 5, 9, 13, 17, 21, and 25 min after rTMS) showed no significant rCBF effects compared to baseline ($p<0.05$, corrected for multiple comparisons over the whole brain). After having identified the time point where rTMS effects were most prominent, we used this contrast to define ROIs for further analysis. Besides the activation cluster at the stimulation site, increased rCBF was present in two other prefrontal areas, i.e. in the VLPFC (BA47) and in the inferior frontal sulcus (BA46/48) which were all located *ipsilateral* to the stimulation site ($p<0.001$, uncorrected; see Table 1). These three regions were then defined as ROIs as described in Materials and methods section.

The two-way repeated measures ANOVA revealed a significant main effect of "time" ($F=2.98$, $df=6,66$; $p=0.01$) and "hemisphere" ($F=6.62$, $df=1,11$; $p=0.03$) in the stimulated region. Importantly, the "hemisphere"×"time" interaction was significant ($F=6.40$,

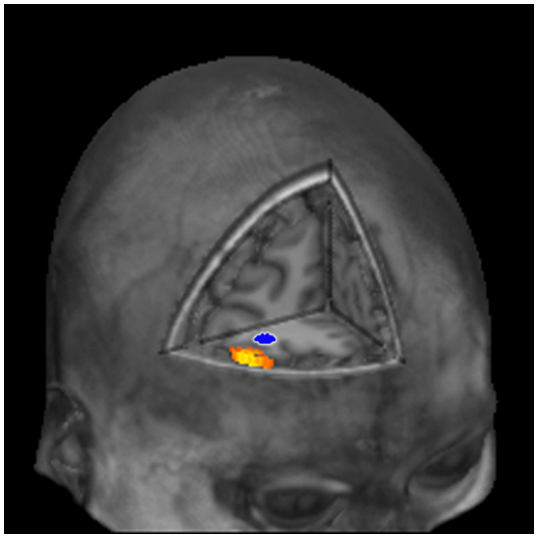

Fig. 2. Three-dimensional illustration depicts the chosen stimulation coordinates ($x=39$, $y=37$, $z=22$; radius=6) and the locus of significant increase in rCBF at the stimulation site. Blue spot, stimulation coordinates; orange spot, significantly increased rCBF.

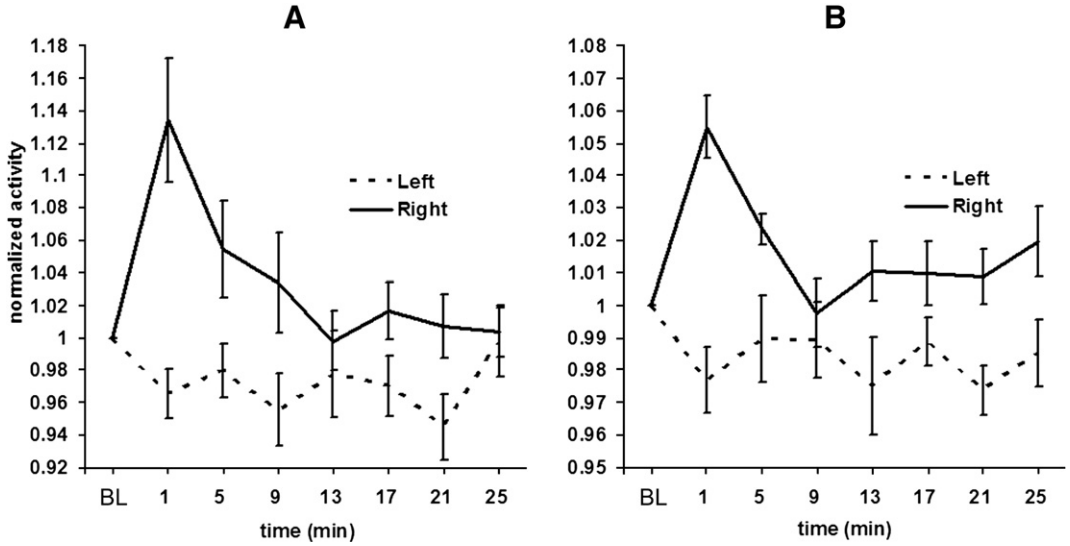

Fig. 3. The time-course (1 to 25 min) of mean normalized activity (±SE) (A) in the stimulated area ($x=50$, $y=48$, $z=16$; BA45/46) and (B) in the VLPFC ($x=42$, $y=42$, $z=-8$; BA47). BL, baseline.

$df=6,66$; $p<0.001$), indicating that the stimulated region shows a time effect of rCBF that is specific to one hemisphere (Fig. 3A). In the VLPFC, a significant main effect of "hemisphere" ($F=15.09$, $df=1,11$; $p=0.003$), but not "time" ($F=1.44$, $df=6,66$; $p=0.21$) was identified. As in the DLPFC, the "hemisphere"×"time" interaction was also significant in the VLPFC ($F=2.68$, $df=6,66$; $p=0.02$) (Fig. 3B). In the inferior frontal sulcus, a significant main effect of "hemisphere" ($F=5.72$, $df=1,11$; $p=0.04$) was identified. However, neither the main effect of "time" ($F=1.38$, $df=6,66$; $p=0.24$) nor the interaction term ("hemisphere"×"time") was significant ($F=0.49$, $df=6,66$; $p=0.81$). Thus, this region shows a hemispheric rCBF effect that is not time specific (see Supplementary data). In the control region (cerebellum), the main effect of "hemisphere" was not significant ($F=3.275$, $df=1,11$; $p=0.098$), while the main effect of "time" was significant ($F=3.28$, $df=6,66$; $p=0.007$). The interaction effect "hemisphere"×"time" was not significant ($F=1.39$, $df=6,66$; $p=0.23$), suggesting that there is no time effect of rCBF specific to one hemisphere in the control region (see Supplementary data). In summary, these findings suggest a spatially and temporally well described specific "off-line" effect of prefrontal rTMS on blood flow in the DLPFC (BA45/46) and the VLPFC (BA47).

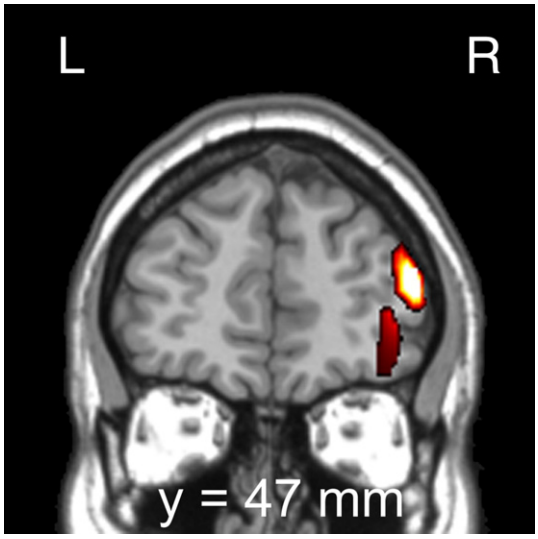

Fig. 4. The time-course of rCBF in the VLPFC (BA47) correlates positively with the time-course of rCBF in the stimulated area (BA45/46). Results are displayed on a coronal section ($y=47$ mm) of averaged anatomical MRI scans (correlation analysis displayed at $p<0.001$, uncorrected; masked with the contrast "1 min>baseline" at $p<0.001$, uncorrected). L, left; R, right.

Fig. 4 shows the results of the masked correlation analysis. A significant positive correlation of the time-course of activity in the stimulated region with the time-course of activity in the VLPFC (BA47) was revealed ($T=8.31$). We found no regions that showed significant negative correlations in the prefrontal cortex (see Supplementary data). Moreover, we found no significant correlation between the time-course of rCBF in the control region (left/right cerebellum) with the time-course of rCBF in the DLPFC (BA45/46).

In summary, we found increased rCBF in the stimulated area, i.e., DLPFC (BA45/46) and in two other prefrontal regions *ipsilateral* to the stimulated site: the VLPFC (BA47) and the inferior frontal sulcus. These regions showed a strong increase in rCBF immediately after rTMS that returned to baseline within 9 min. Moreover, we found that the time-course of rCBF in the VLPFC(BA47) is correlated with the time-course of rCBF in the stimulated area.

Discussion

This study examined the neurophysiological effect of one long-duration train of low-frequency rTMS applied to the right DLPFC. By sequentially measuring rCBF after prefrontal stimulation we were able to investigate three issues in this study: (1) the duration of the "off-line" neurophysiological effect, (2) whether unilateral prefrontal stimulation leads to unilateral or bilateral "off-line" effects and (3) the effects of low-frequency rTMS on remotely connected areas.

The most prominent increase in rCBF was found 1 min after the rTMS train in the right DLPFC (BA45/46) and in the right VLPFC (BA47). While other studies found effects with a delay of several minutes after cessation of the rTMS train (Chouinard et al., 2003;

Johnson et al., 2007), we did not find significantly changed rCBF at later time points, as revealed by whole-brain analyses. One possible explanation is that in the former study a different brain region was stimulated (the left primary and premotor cortex) while in the latter study behavioral effects and not rCBF were reported after low-frequency rTMS of the left DLPFC. In our study, ROI analysis revealed that increased rCBF in the right DLPFC (BA45/46) and right VLPFC (BA47) showed a similar decay over time and returned to baseline values within 9 min. It is possible that the observed rCBF change is the result of unspecific arousal or pain due to rTMS. The cerebellum has previously been reported to positively co-vary with experimentally induced cardiovascular arousal (Critchley et al., 2000). Additionally, it has been reported to be activated during capsaicine induced pain (May et al., 1998). To exclude that no such unspecific effects confounded our results, we additionally analyzed rCBF in both cerebellar hemispheres and found no "hemisphere" × "time" interaction. Moreover, we found no significant correlation of the time-course of rCBF in the cerebellum as our control region with the time-course of rCBF at the stimulation site (BA45/46). It thus seems that low-frequency rTMS indeed induced a temporally well circumscribed "off-line"-rCBF effect on the DLPFC (BA45/46) and the VLPFC (BA47) in our experiment. Thus, as a first conclusion, we find the general rule of thumb confirmed: the effects of 15 min of low-frequency rTMS applied to the right DLPFC last approximately half the duration of the stimulation train. One has to keep in mind, however, that with rCBF we measured indirectly neuronal activity. It might be that rTMS affected neuronal activity for a longer duration and in other regions. Moreover, rCBF was measured while subjects were in a resting state. The effects of "off-line" rTMS on rCBF might be different depending on whether the targeted brain region is involved in the execution of a task or not.

Our results show that stimulating the right DLPFC "off-line" leads to *unilateral* prefrontal but not bilateral effects on blood flow. Most studies that applied rTMS either "off-line" or "on-line" to the DLPFC found no effect under the site of stimulation (Kimbrell et al., 2002; Ohnishi et al., 2004; Speer et al., 2003). In one study however, low-frequency rTMS was applied to the left DLPFC and a *bilateral* activation in the DLPFC was found *during* stimulation (Nahas et al., 2001). In contrast to this, we measured rCBF "off-line" and found only *ipsilateral* prefrontal activation clusters. As a second conclusion, we therefore argue that experimental paradigms in cognitive neuroscience which plan to use "off-line" low-frequency rTMS to affect the functional integrity of an area in the prefrontal cortex could employ a contralateral control stimulation to avoid a side-effects bias.

By measuring rCBF sequentially, we were able to show that the time-course of rCBF in the right VLPFC (BA47) is positively correlated with the time-course of rCBF at the stimulation site (BA45/46). Within the prefrontal cortex, the region in BA47 is the only one that shows a time-course that is correlated with the one in the stimulated area. This finding corroborates the hypothesis of connectivity between dorsal (BA45/46) and ventral aspects (BA47) of the frontal lobes (Petrides and Pandya, 1999). The ventrolateral prefrontal cortex plays an important role in cognitive neuroscience, such as in decision making (Sakagami and Pan, 2007) or emotion regulation (Ochsner et al., 2004). A direct stimulation of this brain area involves great discomfort for the volunteer. As a third conclusion, we thus propose that "off-line" long-train low-frequency rTMS applied to the right DLPFC can be readily used to target remote connected areas, such as the VLPFC via indirect stimulation.

Interestingly, we only found lasting rCBF increases (and not decreases) in the prefrontal cortex. At first sight, this seems difficult to reconcile with studies showing a decrease in cortical excitability after long-train low-frequency rTMS (Chen et al., 1997; Gerschlager et al., 2001; Kosslyn et al., 1999; Maeda et al., 2000; Muellbacher et al., 2000; Wassermann et al., 1998). It is important to note, however, that these findings were exclusively based on studies in primary motor or primary visual cortex.

It is assumed that rTMS as employed in our study induces long term depression (LTD) (Hallett, 2000; Thickbroom, 2007). Since it has been suggested that rCBF changes reflect (pre)synaptic activity changes (Jueptner and Weiller, 1995), one could expect a decrease in rCBF after LTD induction by low-frequency rTMS. While the chosen TMS protocol might indeed have induced a decrease in excitability in the stimulated region, it also might have evoked compensatory regulatory responses in order to maintain normal brain function, which in turn could account for the observed increase.

On the other hand, the observed increased rCBF might also reflect an active inhibition process requiring energy (Ackermann et al., 1984). This interpretation, however, implies that low-frequency rTMS as used in the current study increases the activity of inhibitory interneurons. As several studies suggested, low-frequency rTMS of the primary motor cortex does not lead to increased intracortical inhibition as revealed by subsequent paired-pulse TMS (Brighina et al., 2005; Daskalakis et al., 2006; Fitzgerald et al., 2002; Romero et al., 2002). Based on this evidence it seems less likely that the observed increased rCBF results from an active inhibition process induced by low-frequency rTMS. Irrespective of the underlying physiological mechanisms, one can assume that rTMS application induces a "virtual lesion" simply by adding neural noise to the system (Husain et al., 2002; Walsh and Cowey, 2000; Walsh and Rushworth, 1999). The observed increase in rCBF could then again be interpreted as a regulatory response with a time-course reflecting the duration of the "virtual lesion" effect.

In summary, there are three main results which are critical aspects for the design of a study using brain stimulation in the context of cognitive neuroscience: first, the duration of rCBF changes in the prefrontal cortex is approximately half the duration of the stimulation train itself. Second, right dorsolateral prefrontal stimulation leads to ipsilateral prefrontal rCBF effects. Third, 15 min of "off-line" low-frequency rTMS of the dorsal aspects of the frontal lobe (BA45/46) leads to rCBF changes in areas assumed to be effectively connected to the stimulation site, such as the VLPFC (BA47).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2008.04.172.

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