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ROLE OF THE PREFRONTAL CORTEX IN THE FOREPERIOD EFFECT: TMS EVIDENCE FOR DUAL MECHANISMS IN TEMPORAL PREPARATION

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Abstract

The involvement of right dorsolateral prefrontal cortex (rDLPFC) in explicit temporal processing is well-documented. Conversely, the role of this area in implicit temporal processing (e.g., foreperiod effect) is still poorly understood.

The foreperiod (FP) effect, usually observed when a range of variable FPs occurs randomly and equiprobably, consists of RTs decreasing as the FP increases. Moreover, in such paradigms, RTs increase as a function of the preceding FP (i.e., sequential effects). Patients with lesions of the rDLPFC do not show the typical FP effect [Stuss and others. 2005. Multiple frontal systems controlling response speed. Neuropsychologia 43(3):396-417].

The present study aimed to replicate these results in healthy adults using Transcranial Magnetic Stimulation (TMS), and to further investigate whether any change of sequential effects follows a reduction of the FP effect. The results of two experiments (with simple and choice RT tasks, respectively) indicate that the FP effect was significantly reduced after TMS over the rDLPFC, while no effect was observed after stimulation of a left contralateral site and the right angular gyrus. Conversely, sequential effects were not influenced by TMS. A dual-process model of the FP phenomena is proposed to interpret the dissociation found between the two effects.

Keywords: Dorsolateral Prefrontal, Implicit Temporal Processing, Sequential effects, Theta Burst, Variable Foreperiod.

A number of models postulate the existence of an anterior attentional system with a set of supervisory functions (e.g., Norman and Shallice, 1986; Posner & Petersen, 1990). Recent evidence suggests a fractionation of these high-level functions within a network of different functional prefrontal areas (e.g., Shallice, 2004; Stuss and others, 2005). However, according to an opposite view, each prefrontal area has an undifferentiated and equi-potential role, as different cognitive demands usually involve common, or at least overlapping, prefrontal regions (e.g., Duncan and Owen, 2000). The present study is intended to provide a specific contribution to this more general debate, by investigating the prefrontal involvement in a basic cognitive capacity, preparation over time. Although preparation is a ubiquitous cognitive process, the way in which it evolves over time, how the cognitive system makes use of temporal information to optimize behaviour, and which brain regions are engaged during preparation, are all issues which still remain unresolved.

A typical paradigm employed to study the relationship between time and non-specific preparation is the Variable Foreperiod (FP) paradigm. In a Reaction Time (RT) paradigm, the FP is the unfilled time-interval between the Warning Stimulus (WS) and the stimulus requiring a response, the so-called Imperative Stimulus (IS). When FPs at a number of points within a fixed range occur randomly over trials but with the same a priori probability, RTs are longer for shorter FPs and shorter for middle and longer FPs[1]. This is the variable FP effect (Woodrow 1914; see Niemi and Näätänen 1981, for a review). The traditional explanations of this phenomenon have attributed it to strategic processes. On these approaches, the FP effect is explained by assuming the existence of a process which continually checks the conditional probability of IS occurrence. This process leads to an increase over time in the strategically controlled state of preparation, if the IS has failed to occur so far during the FP (e.g., Drazin 1961; Näätänen 1970).

Insert Footnote 1 about here

Moreover, sequential effects are also usually observed with this paradigm: longer FPs on the preceding trial produce slower RTs on the current one (Karlin 1959; Niemi and Näätänen 1981). This is particularly the case for the shortest current FPs. Hence, the sequential effects usually found are asymmetrically biased towards the shortest FPs in the range used. Traditionally, the sequential effects are explained by assuming that the cognitive system reaches peak preparation strategically at the same FP as the previous trial (Alegria 1975). Additionally, when a FP on the current trial is longer than on the previous one, it is assumed that participants can voluntarily extend the period of optimal preparation (Karlin 1959; Thomas 1967) or cyclically reprepare (Baumeister and Joubert 1969; Alegria, 1975). This repreparation/maintenance hypothesis accounts for the asymmetry, in that sequential effects occur on the 'long-short' FP sequences but not on the 'short-long' ones.

However, recent empirical evidence presents a challenge to the strategic accounts. Los and van den Heuvel (2001) designed a temporal cueing paradigm with a variable FP design. In their Experiment 2, they used valid (80%) and invalid (20%) signals cueing the FP interval. With a valid cue, participants could intentionally prepare for the cued FP and, consequently, the sequential effects were drastically attenuated. The most impressive results, however, were obtained with an invalid cue for the FP duration. In particular, when an invalid cue for a *long* FP preceded an actual current *short* FP, the costs of not having prepared in advance for that short FP are not constant. They vary as a function of the FP that occurred on the preceding trial. Sequential effects are stronger as compared with those occurring after a validly cued FP. If sequential effects were fully strategic in nature, as traditional accounts claim, there would be no reason for them to influence costs after invalid cues. For these reasons, Los and van den Heuvel (2001; see also Los and others 2001) propose an alternative account, in which both the

FP and the sequential effects are integrated in a common theoretical framework based on conditioning mechanisms. For each FP, a level of activation is adjusted in a way that obeys the learning rules of trace conditioning (Machado 1997). It is assumed that, if any FP occurs on trial *n-1*, then the conditioned strength of the representation of each FP in the range will be modified so that it will be (i) increased for that FP, (ii) not influenced for longer FPs, (iii) decreased for shorter FPs, because of a need to avoid anticipation responses. Thus, if an equally long FP occurs on trial *n*, the corresponding RT will tend to be faster than if a shorter FP had occurred. This conditioning view has the advantage of linking the FP effect closely to the sequential effects in a single-process account, because RT on trial *n* is a function of the conditioning influences produced on trial *n-1*.

On the other hand, the involvement of strategic control in a variable FP paradigm was indirectly supported by neuropsychological findings. As shown in a recent neuropsychological study (Stuss and others 2005), patients with lesions in the right dorsolateral prefrontal cortex (DLPFC) fail to show the typical FP effect, unlike both control participants and other subgroups of prefrontal patients. Stuss and colleagues suggest that the right DLPFC is likely to be the region responsible for the strategic process producing the FP effect, which controls the state of preparedness by checking the conditional probability of IS occurrence. This account fits a range of studies which attribute a monitoring role to the right DLPFC (Coull and others 1998; see Fletcher and Henson 2001; Shallice 2004, for reviews). Unfortunately, the sequential effects were not considered in Stuss and colleagues' (2005) study. Hence, without an additional investigation of the sequential effects produced by the patients, the lack of FP effect shown can alternatively be interpreted as a failure in the conditioning processes, according to the conditioning view (Los and van den Heuvel 2001).

The aim of the present study is twofold: concerning both the anatomical and the functional bases of the FP phenomena. From an anatomical point of view, the aim was to

investigate whether the neuropsychological results (Stuss and others 2005) could be reproduced in healthy adults by means of Transcranial Magnetic Stimulation (TMS). In addition, however, the study could allow one to establish the role of the right DLPFC not only in the FP effect, but also with respect to the sequential effects, which have not been investigated neuropsychologically. In addition, the role of the right angular gyrus (AG) in the FP phenomena was investigated here, since this area is often associated with temporal processing found in fMRI and TMS studies (Coull and others 1998; Rao and others 2001; Lewis and Miall 2003; Alexander and others 2005). It can be argued that these studies utilize tasks which require explicit time processing while the time processing required in an FP paradigm is implicit. However, a recent study has also demonstrated anticipatory activity revealing an internal representation of both elapsed time and the probability of the stimulus occurrence in the macaque parietal lobe during an implicit time processing task similar to the variable FP paradigm (Janssen and Shadlen 2005; see also Onoe and others 2001).

From the functional point of view, TMS can provide a strong test of the various cognitive models of the FP phenomena. If both the FP and the sequential effects are influenced by the TMS on right DLPFC, a common mechanism is likely to underlie them, as predicted by the conditioning view (Los and van den Heuvel, 2001). If instead the FP effect only is modified, this would be evidence for a dual-process theory of the FP phenomena. In order to test these possibilities two experiments were designed with a simple and a choice RT task (experiments 1 and 2, respectively) and a theta burst stimulation (TBS) off-line paradigm of repetitive TMS, which has been demonstrated to transiently decrease cortical activity in the stimulated area (Huang and others 2005). Moreover, the range of FPs used in Stuss and colleagues' (2005) study (i.e., 3-7 seconds), might suggest the alternative explanation of a deficit of the vigilance system in maintaining attention over a long period of time, instead of a monitoring process, in the case of right prefrontal lesions. For this reason, a much shorter FP range was

used (i.e., 0.5, 1 and 1.5 sec), to discard vigilance-related accounts of a possible modulation of the FP effect.

Experiment 1

In experiment 1 a simple RT task was used in order to study the FP phenomena in their simplest form. For this purpose, a range of FPs (i.e. 0.5, 1.0 and 1.5 sec) was employed in a standard variable FP paradigm. A repetitive TMS paradigm was used to investigate the role of the right DLPFC in the FP phenomena. In order to control the specificity of any effect obtained to the right DLPFC, two additional areas were stimulated during different sessions, namely a site in the left DLPFC and another in the right AG.

Method

Participants

Nine volunteer participants, 3 females and 6 males, took part in the experiment. They were 31 years old on average (range = 24-43). All of them were right-handed with an average score of 92 on the Edinburgh Handedness Inventory (Oldfield 1971). All had normal or corrected-to-normal vision, and no auditory or neurological impairment. This study was approved by the UCL Committee on the Ethics of Human Research.

Apparatus and Materials

The experiment was conducted on a PC. Stimuli were presented on a 19” monitor with a 100-Hz refresh rate. Participants viewed the display at a distance of about 60 cm from the centre of the monitor, with the index finger of their dominant hand resting on the keyboard spacebar. The auditory warning stimulus (WS) was a 1500 Hz pure tone, presented for 50 ms through bilaterally-located speakers. All visual stimuli were presented on a black background.

A centrally presented cross, consisting of two yellow crossed bars 1.0 x 0.5 cm in size, served as a fixation stimulus. The imperative stimulus (IS) was a downward pointing white arrow 2 cm long, which consisted of a 1.5 x 1 cm bar attached to a 0.5 cm arrowhead with a maximum width of 2 cm. Two blocks were presented during each session to each participant, one before and the other after TMS. In each block, three FPs of 0.5, 1.0 and 1.5 sec, respectively, were presented for an equal number of trials (i.e. 48 trials each), randomly drawn from a rectangular probability distribution. Each FP was preceded with the same probability by a FP of 0.5, 1.0 and 1.5 sec.

Procedure and Task

Figure 1 displays the hierarchical organization of the experiment 1. The experiment consisted of 3 sessions performed in 3 different days within one week, one for each area stimulated (see below). Each session consisted of 2 blocks of 144 trials each. The first block was run before the TMS to measure the baseline performance. The second block was run after the TMS to measure its effects on the behavioural performance. Unpublished data from our laboratory show that the learning period for the FP phenomena, if any, is very brief, as after an initial block of 60 trials the FP and sequential effects are already present with the same magnitude as in subsequent blocks. For this reason, we could be confident that the performance of the baseline block would not influence the performance on the post-TMS block. Participants were tested individually in a silent and dimly light room. They received written instructions explaining the simple RT task. A trial started with the presentation of the fixation cross together with the WS. The onset of WS marked the beginning of the FP. When the FP ended, the fixation cross disappeared, and the IS was presented at the centre of the screen. Participants were instructed to respond as fast as possible to the IS by pressing the spacebar with the index finger of their right hand. The IS was removed by the response key

press or after a deadline of 1.5 sec. After a blank interval of 1 sec, a new trial started. Nine practice trials were given at the beginning of the test. An experimental session lasted about 25 minutes each day (i.e., 6-7 minutes per block plus some minutes after the baseline block needed to find the site coordinates in the brain).

Insert Figure 1 about here

TMS protocol

Locations for TMS were determined using the Brainsight TMS-MRI co-registration system (Rogue Research, Montreal, Canada), through conversion of the MNI stereotaxic coordinates to participant's normalised brain using the software SPM2. For each session, participants underwent the co-registration in the interval between the two pre- and post-TMS blocks, in order to find the coordinates of the area of interest in their real brain. Those coordinates were taken from an fMRI study by Lewis and Miall (2003), in which activation of the right and left DLPFC and of the right AG was found during a temporal discrimination task for both sub- and supra-second intervals. For each participant and session, one area was stimulated after the performance of the pre-TMS baseline block. The areas to be stimulated were located in the right DLPFC (MNI stereotaxic coordinates: 48, 42, 24), in a control area on the left DLPFC (the mirrored contralateral site, i.e., -48, 42, 24) and in the right AG (48, -45, 48), respectively (see Fig. 2). The order in which the 3 areas were stimulated was counterbalanced across participants, such that each area was stimulated in the first day session on an equal number of participants.

Insert Figure 2 about here

Participants wore a latex swimming cap on which the location found in the co-registration procedure was marked with a phosphorescent spot. Stimulation was produced through a MagStim Super Rapid stimulator with 4 external boosters with a maximum output of approximately 2 T (MagStim, Whitland, UK). A figure-of-eight 50-mm coil was used for the stimulation with the center of the coil positioned over the marked spot such that the windings were at 90° to the scalp and the handle pointed vertically.

An offline TMS paradigm was chosen rather than an on-line one to prevent any exogenous influence of the sound and the proprioceptive sensation given by the TMS on the RTs (e.g., Terao and others 1997) and hence on the FP phenomena. In each session, the TMS parameters were those of the continuous TBS, consisting of a burst of 3 pulses at 50 Hz (i.e., 20 ms between each stimulus), which was repeated at intervals of 200 ms for 20 seconds (giving a total of 300 pulses). The output strength of the TMS was set to 80% of the participant's active motor threshold, defined as the minimal intensity of stimulation capable of inducing a visible twitch of the contralateral first dorsal interosseus in at least 6 trials out of 10, by means of a single pulse delivered at the best scalp position over motor cortex. During the calculation of the active motor threshold, the participant's dominant hand was in a moderately contracted position and the thumb and index fingers were in opposition. Previous studies (Di Lazzaro and others 2005; Huang and others 2005) have demonstrated that this TBS protocol temporarily produces reduced excitability of motor cortex outlasting the period of actual TMS. With 20 seconds stimulation, the time window of reduced excitability was estimated to last up to 20 minutes.

Data Analysis

Trials on which the RT was outside the 100-1000 ms range and trials where anticipated responses were made (viz. ones occurring before the IS) were discarded from further analyses.

In addition, the first trial of each block was eliminated. Mean RTs for each participant and condition were analysed by repeated-measures ANOVAs.

As a first step, three separate repeated-measures ANOVAs have been conducted contrasting baseline against post-TMS blocks separately for each site stimulated during each session (right DLPFC, left DLPFC, right AG). The within-subject independent variables considered in these preliminary analyses included FP on the current trial (FP_n = 0.5, 1.0 and 1.5 sec), FP on the preceding trial *n-1* (FP_{n-1}) and the TMS block (Baseline vs post-TMS). The dependent measure was the mean RT.

In order to investigate differences across TMS sessions, a subsequent overall repeated-measures ANOVA was then performed with FP_n, FP_{n-1}, and TMS site (right DLPFC, left DLPFC and right AG) as the within-subjects variables. The dependent variable chosen in this overall ANOVA was the degree of change in mean RTs as a result of stimulation at each site compared with the mean RTs of the pre-TMS baseline block of the same session (with 100% representing no RT change, a value >100% representing a slowing down, and one <100% indicating a speeding up)[2].

For the significant effects, post-hoc Tukey honestly significant difference comparisons were performed, in order to see which comparisons accounted for the effects. An effect was defined as significant if its corresponding α-level was below .05. The F-test was adjusted by the Greenhouse-Geisser ε correction when the Mauchley sphericity test was significant.

Insert Footnote 2 about here

Results

The first trial of each block (0.7 %), trials involving anticipated responses (RT before IS onset: 1.9 %), trials involving premature responses (RT < 100 ms: 0.5 %), and trials with

delayed responses (RT > 1000 ms) or without responses (0.03 %), were discarded from further analyses. Fewer than 3.2 % of trials were excluded, with no difference across conditions.

Behavioural Results

The FP and sequential results were produced as expected. The following effects were significant in ANOVAs conducted on the 3 sessions separately (see Fig. 3). First, the main effect of FP_n was obtained [$F(2, 16) = 28.7$, $p < .001$; $F(1.1, 9.1) = 40.1$, *Adj.* $p < .001$; $F(2, 16) = 34.1$, $p < .001$, for right DLPFC, left DLPFC and right AG, respectively]. Post-hoc Tukey HSD comparisons showed that RTs were slowest for the shortest FP of 0.5 sec as compared to the middle and longest FPs (for all, $p < .001$), but there was no difference between the RTs for FPs of 1.0 and 1.5 sec in any session. The main effect of FP_{n-1} also reached significance [$F(1.1, 8.8) = 5.5$, *Adj.* $p < .05$; $F(1.2, 9.9) = 15.3$, *Adj.* $p < .01$; $F(1.3, 10.1) = 17.2$, *Adj.* $p = .001$, for right DLPFC, left DLPFC and right AG, respectively]. The post-hoc comparisons showed that current RTs were slower following a longest FP_{n-1} trial than a shortest FP_{n-1} trial (for all, $p \leq .01$). The FP_n x FP_{n-1} interaction, concerning asymmetry of sequential effects, was also significant [$F(4, 32) = 23.6$, $p < .001$; $F(4, 32) = 11.4$, $p < .001$; $F(2.4, 19.6) = 6.5$, *Adj.* $p < .01$, for right DLPFC, left DLPFC and right AG, respectively]. This effect was primarily due to the differential contribution of the FP_{n-1} to the RT at each of the 3 current FPs, being greatest for the shortest FP_n and smallest, virtually absent, for the longest FP_n, as confirmed by post-hoc comparisons.

TMS Effects: separated ANOVAs for each TMS site

No TMS block main effect was observed for any site of stimulation, indicating that RTs were not non-specifically modified by the TBS. More critically, the TMS block x FP_n

interaction was significant only for the right DLPFC session [$F(2, 16) = 7.2$, $p < .01$], indicating that the FP effect was reduced in the post-TMS block as compared with the baseline block during the right DLPFC session. This conclusion was corroborated contrasting the RT difference between the shortest and the longest FP_n in the baseline block (43 ms) and the same RT difference in the post-TMS (26 ms) by means of planned comparisons ($p < .001$). In addition, there was a tendency for a TMS x FP_{n-1} interaction in the right DLPFC session [$F(2, 16) = 3.5$, $p = .054$], suggesting that the effect of the FP_{n-1} was slightly reduced after TMS with respect to the baseline block. However, the TMS block x FP_n x FP_{n-1} three-way interaction was not significant in any session (for all, $p > .3$), indicating that the sequential effects were not significantly modulated by the TMS.

Insert Figure 3 about here

TMS Effects: Overall ANOVA

The only significant effect obtained in the overall ANOVA was the interaction between TMS site and FP_n [$F(4, 32) = 2.8$, $p < .05$], indicating that the FP effect was selectively modulated after TMS over the right DLPFC (see Fig. 4). In this case only, indeed, the RTs on the longest FP_n were slower with respect to the baseline (104%) while the RTs on the shortest FP_n were faster (97%), the difference between these two values being significant following post-hoc Tukey comparisons ($p < .01$). It is noteworthy that this modulation goes in the opposite direction with respect to the FP effect itself, slowing RTs down on the longest FP_n and speeding them up on the shortest FP_n. Notably, no TMS modulation was found for the sequential effects, as indicated by the lack of significance for the TMS site x FP_n x FP_{n-1} three-way interaction ($p = .45$).

Insert Figure 4 about here

Discussion

The FP effect and the asymmetric sequential effects, usually found in a variable FP paradigm, were replicated in experiment 1. Moreover, a role of the right DLPFC was demonstrated for the FP effect. Following TMS over the left DLPFC and the right AG, no significant changes were observed with respect to the baseline. On the other hand, after TMS over the right DLPFC, a reduction in the FP effect was observed, confirming the role of this area in the occurrence of this effect, as already shown by a recent neuropsychological study (Stuss and others 2005). This result is interesting per se but cannot be used to corroborate any dual-process model of the FP phenomena. A dissociation between the FP and the sequential effects was not clearly obtained in this experiment, because the effect of the FP_{n-1} also showed a tendency towards being reduced after the TMS over the right DLPFC.

As the reduction of the cortical excitability of the motor cortex reaches a maximum from 7 to 14 min after TBS (Di Lazzaro and others 2005; Huang and others 2005), a similar time course can be expected in the case of the right DLPFC. For this reason, in the second experiment two blocks of trials were performed by participants in order to cover, apart from an initial 6 min period similar to experiment 1, an additional subsequent period when the stimulation effects are supposed to be at their greatest.

Experiment 2

Experiment 2 was designed to be similar to experiment 1, with two exceptions. First, there were two blocks of trials instead of one after the TMS. This change was made in order to cover the whole period in which the long-lasting effects of TBS operate, including the most critical interval of 7-14 min post-TMS, possibly increasing the sensitivity of experiment.

Second, a two-choice RT paradigm was chosen in order to avoid anticipation and ceiling effects which might occur during a simple RT task, such as that used in experiment 1; such effects could have partially obscured any TMS effects. It should be noted that, although the additional stage of response selection is required by a choice RT task, FP effect is held to involve *non-specific* preparation processes only. Indeed, the typical FP phenomena are basically similar for both simple and choice RT tasks (Los and van den Heuvel, 2001), and the right prefrontal lesion effect is found for both paradigms (Stuss and others 2005).

Method

Participants

Nine volunteer participants, 4 females and 5 males, took part in experiment 2. They were 30 years old on average (range = 22-43). All of them were right-handed (with an average score of 83 at the Edinburgh Handedness Inventory). All had normal or corrected-to-normal vision, and no auditory or neurological impairment. Three of them had participated in the experiment 1 (at least one month before).

Apparatus and Materials

The apparatus and materials were the same as in experiment 1 except that, on each trial, the IS appeared with the same probability to the right or left of the fixation cross at a distance of 7.5 cm (center to center).

Procedure and Task

The task was to perform a spatially compatible response to the IS by pressing a right or left key on the computer keyboard (‘F’ or ‘J’, respectively) as fast as possible. Experiment consisted of 3 sessions performed on 3 different days within a maximum period of a week.

Each session consisted of 3 blocks of 144 trials each. During each session, the first block was run before the TMS to measure the baseline performance and the second and third blocks were run consecutively after the TMS. The whole experimental session lasted about 35-40 minutes.

Data Analysis

The same criteria as in experiment 1 were used for the analysis of the data obtained in experiment 2. In addition, only trials with correct (spatially compatible) responses to the imperative stimulus were considered for the RT analyses. Moreover, preliminary analyses including the spatial position of the IS (and of the response) did not give rise to any interaction between this factor and that of the TMS site factor. For this reason, the spatial position factor was collapsed in the following analyses.

As a first step, 3 separate repeated-measures ANOVAs were conducted, one for each stimulated site (right DLPFC, left DLPFC and right AG). The within-subject independent variables considered in these preliminary analyses included FP on the current trial (FP_n = 0.5, 1.0 and 1.5 sec), FP on the preceding trial *n-1* (FP_{n-1}) and the TMS block (Baseline, first and second post-TMS blocks). The dependent measure was the mean RT.

A subsequent overall repeated-measures 3x3x2x3 ANOVA was also performed with FP_n, FP_{n-1}, TMS block (first and second post-TMS blocks) and TMS site (right DLPFC, left DLPFC, right AG) as the within-subjects variables. The dependent variable chosen in this overall ANOVA was the percentage of change of mean RTs collected after the first and second post-TMS blocks in each session compared to the mean RTs of the pre-TMS baseline of the same session. As in the experiment 1, the F-test was adjusted by the Greenhouse-Geisser procedure when appropriate.

Results

The first trial of each block (0.7 %), trials involving anticipated responses (RT before IS onset: 0.08 %), trials involving premature responses (RT < 100 ms: 0.02 %), and trials with delayed responses (RT > 1000 ms) or without responses (0.02 %), and trials with an incorrect response on the spatial compatibility task (0.8 %) were discarded from further analyses. Fewer than 1.8 % of trials were excluded.

Behavioural Results

The following effects were significant in ANOVAs conducted on the 3 sessions separately (see Fig. 5). A main effect of FP_n was obtained [$F(2,16) = 10.1$, $p = .001$; $F(1.3, 10.1) = 15.8$, *Adj.* $p < .01$; $F(2, 16) = 17.3$, $p < .001$, for the right DLPFC, left DLPFC and right AG, respectively]. Post-hoc comparisons showed that RTs were slowest for the shortest FP of 0.5 sec as compared to the middle and longest FPs (for all, $p < .01$). Moreover, the main effect of FP_{n-1} was also significant [$F(2,16) = 16$, $p < .001$]. The post-hoc comparisons showed that current RTs were slower following a middle FP_{n-1} trial than a shortest FP_{n-1} trial and, in turn, following a longest FP_{n-1} trial than a middle one (for the right AG, the difference between the middle FP_{n-1} and the longest one was not significant, for all the other comparisons, $p < .05$). The FP_n x FP_{n-1} interaction, concerning the asymmetric sequential effects, was also significant [$F(1.8, 14.8) = 5.1$, *Adj.* $p = .02$; $F(4, 32) = 12.7$, $p < .001$, for the right DLPFC and left DLPFC, respectively; and a tendency for the right AG, $F(1.5, 12) = 3.9$, *Adj.* $p = .059$]. This effect was principally due to the differential contribution of the FP_{n-1} to the RT on each of the three current FPs, being greatest for the shortest FP_n and smallest for the longest FP_n, as confirmed by post-hoc comparisons.

TMS Effects: separated ANOVAs for each TMS site

No TMS block main effect was observed for any site of stimulation, indicating that RTs were not non-specifically modified by the TBS. As for experiment 1, the TMS block x FP_n interaction was significant for the right DLPFC session only [$F(4, 32) = 4.5$, $p < .01$]. The FP effect was reduced in the first and second post-TMS block with respect to the baseline, as demonstrated by subsequent planned comparisons. Significant planned comparisons were obtained contrasting the RT difference between the shortest and the longest FPs in the baseline condition and the same RT difference in the first and in the second blocks post-TMS of the right DLPFC (for all, $p < .001$). However, post-hoc comparisons indicated that the differences between RTs in any of the FPs in the baseline contrasted with the same FPs in the post-TMS blocks were not significant (for all, $p > .1$). As in experiment 1, this pattern indicates that the reduction of the FP effect was not due to a specific effect on RTs for the shortest, middle or longest FP, but instead to an overall effect which acts by attenuating the FP effect as a whole. Thus, the difference between the RT on the shortest FP_n and on the longest FP_n decreased from 33 ms in the baseline block to 22 ms in the first post-TMS block, to reach 15 ms in the last post-TMS block. No other effect was significant. In particular a lack for a three-way TMS block x FP_n x FP_{n-1} interaction in all the 3 sessions (for the left DLPFC, $p > .8$; for the right AG, $p > .6$; for the right DLPFC, $p > .2$) suggested that TMS did not modulate sequential effects.

Although no three-way interaction was observed in any analysis, visual inspection of Figure 5 suggests, for the right DLFPC session, the presence of more symmetric sequential effects in the last TMS block with respect to the baseline. The three-way interaction may be hidden by the number of conditions introduced in the ANOVA. To statistically assess this possibility, a subsequent 3x3x2 ANOVA was performed for the right DLPFC session, with FP_n, FP_{n-1} and TMS block as within-subjects variables, contrasting the baseline block with the second TMS block only. This analysis was justified by the fact that the TMS effect was

expected to reach a maximum during this second block (i.e., from 7 to 14 minutes post-TMS; Huang and others, 2005). Apart from the main effects of FP_n and FP_{n-1} and the interaction between these two factors, which confirm the previous analysis, this analysis produced a significant three-way interaction [$F(4, 32) = 2.7$, $p < .05$]. To confirm that the difference was due to the presence of symmetric sequential effects in the second post-TMS block, further planned comparisons have been carried out. Specifically, these comparisons contrasted the difference between the RT on the longest FP_n preceded by the longest FP_{n-1} and the RT on the same longest FP_n preceded by the shortest FP_{n-1} in the baseline with the same difference in the second post-TMS block. This analysis was significant ($F(1, 8) = 13.9$, $p < .01$), confirming that, in the second post-TMS block, sequential effects were basically symmetric, as they were also present on the longest FP_n.

Insert Figure 5 about here

TMS Effects: Overall ANOVA

The main effect of the FP_n was significant [$F(2, 16) = 5.1$, $p < .05$]. Post-hoc comparisons indicated that post-TMS RTs were slower after a long FP_n and faster after a short FP_n with respect to the baseline values (101% vs. 99%; $p < .05$). More importantly, an interaction between TMS site and FP_n was obtained [$F(4, 32) = 3.5$, $p < .05$], indicating that the FP effect was selectively attenuated after TMS on the right DLPFC (see Fig. 6). In this case only, the RTs on the longest FP_n were slower with respect to the baseline block (103%) while the RTs on the shortest FP_n were slightly faster (99%), the difference between these two values being significant on post-hoc Tukey comparisons ($p < .05$). This effect demonstrates a reduction of the FP effect selectively after the TMS to the right DLPFC, replicating the results of experiment 1. No other effect was significant. As in the first experiment, the left DLPFC

and the right AG turned out to act as TMS control sites because no effect involving TMS was observed in these analyses.

Insert Figure 6 about here

Discussion

The results of experiment 2 confirm those of experiment 1. In particular, the reduction of the FP effect as a consequence of TMS acting specifically on the right DLPFC was replicated while no TMS effect was obtained on the left DPLFC and the right AG. This result confirms the role of the right DLPFC for the occurrence of the FP effect (see Stuss and others 2005).

On the other hand, the sequential effects were not reduced by the TMS in the right DLPFC, clearly suggesting that the non-significant tendency found in experiment 1 was likely to be due to noise. As a dissociation between the two effects has been obtained, the hypothesis of a common mechanism underlying both effects is not supported. Interestingly, the sequential effects become more symmetric during the second post-TMS block of trials on the same area. This was confirmed by the presence of a significant FP_n x FP_{n-1} x TMS block interaction, although this was obtained only for a direct comparison between the baseline block and the second post-TMS one, namely the block in which the effects of the TBS would be expected to be stronger (see Huang and others 2005). Such evidence, although not confirmed by the analysis across TMS sessions, corroborates the pattern found in a developmental study of the FP phenomena by Vallesi and Shallice (in preparation, see general discussion). As in the youngest children of that study (i.e., 4-5 years old), whose DLPFC is presumably not yet mature, after 6-7 minutes from TMS of the right DLPFC the sequential effects become more symmetric while the FP effect decreases.

General Discussion

The FP effect can be briefly described as a negatively accelerating RT-FP function, obtained when a range of FPs is randomly administered with the same a priori probability in simple or choice RT tasks. The present study was primarily designed to investigate the anatomical basis of the FP effect by means of TMS. To this purpose, in the experiment 1 a variable FP paradigm with a simple RT task was performed by 9 volunteers in two blocks, before and after TMS of three sites, right DLPFC, left DLPFC and right AG (one per each session day). A possible limitation of experiment 1 was that testing did not take place in the most critical period of the TMS effect when the TBS is employed (i.e., 7-14 min, see Huang and others 2005). This limitation was overcome in the second experiment, where 9 participants carried out two experimental blocks following TMS. Stuss and colleagues (2005) found a right frontal lesion effect on variable FP paradigms using choice RTs as well as simple RTs. So, another change introduced in the second experiment was the use of a choice RT task instead of the simple RT task used in the experiment 1.

Both experiments of the present study provide clear evidence for a role of the right DLPFC in the production of the FP effect. Specifically, a 20 sec off-line repetitive TMS (i.e., TBS) over this area, compared to the pre-TMS baseline level and to an analogous stimulation on two other sites (i.e., left DLPFC and right AG), is enough to significantly reduce the size of the FP effect for the post-TMS period investigated. This period was about 6 minutes long for the simple RT task in experiment 1, and 15 minutes long for the choice RT task in experiment 2. These results fit well with existing neuropsychological literature. As suggested by Stuss and colleagues (2005), the right DLPFC seems to be the location of a process critical for the FP effect, because patients with lesions of this region do not show the typical FP effect. Moreover, a link between the FP effect and dopaminergic activity has been demonstrated in neuropsychological studies. The dopaminergic system is a neurotransmitter

system massively present within the DLPFC. Drug-free schizophrenic patients, for example, who have increased levels of dopamine (see Kapur 2003, for a review), show an exaggerated variable FP effect (Zahn and others 1963), whereas Parkinsonian patients, who suffer from deficiencies in dopamine levels (e.g., Rakshi and others 1999), have a reduction of this effect (Jurkowski and others 2005).

The short FP range used in the present study (i.e., 0.5, 1 and 1.5 sec) allows us to discard accounts relating the reduction of FP effect after TMS of the right DLPFC to vigilance or alertness (e.g., see Posner and Petersen 1990), such as a deficit in maintaining a high level of preparation for a long time interval. This account would be also in contrast to the results obtained by Stuss and colleagues (2005) on prefrontal patients. In that study, indeed, right frontal patients showed no FP effect with a variable FP paradigm. Noteworthy, with a fixed FP paradigm, their performance was comparable, even for the longest FPs in the range, to that of other frontal patients, apart from medial frontal ones.

The FP effect is probably due to a process of endogenous preparation, analogous to that already described by some traditional accounts (e.g., Näätänen 1970). This process checks the information for the non-occurrence of the IS, using the information derived from the increasing conditional probability of the IS occurrence as time elapses in order to enhance preparation. As in right DLPFC patients (Stuss and others 2005), it is likely that this checking process does not operate efficiently after TMS over this area. The right DLPFC region controlling such process would be permanently damaged in the neuropsychological patients studied by Stuss and colleagues and compromised transiently in the present study using TMS.

In partial support of this view, activation of the right DLPFC has already been demonstrated in a number of brain imaging and TMS studies during tasks dealing with temporal processing, such as time discrimination tasks (e.g. Rao and others 2001; Lewis and Miall 2003) and time reproduction tasks (e.g. Basso and others 2003; Koch and others 2003;

Jones and others 2004). It can be argued that these tasks are different in nature from the variable FP task, in that the former overtly require temporal processing while the latter do not. However, what the two kinds of tasks may have in common is the monitoring of temporal information, which is explicitly required by time reproduction and discrimination tasks, and implicitly exploited during the variable FP paradigm in order to reach an optimal level of preparation (Näätänen 1970). As the results of the present study and of the literature empirically suggest, this monitoring process is conceivably subserved by the right DLPFC.

The present study also investigated the role of the right DLPFC in the sequential FP effects. These well-known effects consist of an increase in RT as the preceding FP becomes longer. The sequential effects are usually asymmetrically more pronounced for the shortest FPs in the range employed, while they are virtually absent for the longest FPs. A tendency ($p = .054$) for a reduction of the effect of FP_{n-1} was found after stimulation of the right DLPFC in the first experiment which used a simple RT task. This tendency was, however, no different following TMS of right DLPFC from that of the other two sites employed (see results of the overall ANOVA). Moreover, in the experiment 2, a dissociation between the FP effect and the sequential effects was obtained after stimulating the right DLPFC: the FP effect was significantly reduced while the sequential effects were not influenced in magnitude. Thus, we obtained site controls (i.e., right DLPFC vs. all other sites and no TMS) and a task control for our effects (i.e., FP vs. sequential effects dissociation).

Moreover, in the second block after TMS of the right DLPFC, when the TMS effects are supposed to be at their strongest (Huang and others 2005), the sequential effects were more symmetric with respect to the baseline block, as confirmed by a subsequent ANOVA. Symmetric sequential effects would not be expected according to the conditioning view (Los and van den Heuvel, 2001). This account predicts that the sequential effects, if present, must inevitably be asymmetric, due to a main role of extinction on the activation strength of the

shortest FPs, and of reinforcement on the activation strength of longest FPs. The observation of symmetric sequential effects when the FP is attenuated may be tentatively accounted for by a recently proposed dual-process model (Vallesi and Shallice, in preparation). According to this model, the sequential effects per se can be explained by assuming an enhancement in arousal following a short FP_{n-1} and a decrease following a long FP_{n-1}, whatever the current FP_n. In support of this view, tonic influence of the FP_{n-1} on preparation was electrophysiologically tracked in a recent study by Los and Heslenfeld (2005). In that study, the Contingent Negative Variation (CNV) was used as a covert index of non-specific preparation, during a variable FP paradigm employing temporal cuing. The results show phasic effects of cuing on the CNV amplitude at the end of the short FP_n. In that case, the CNV was more negative following signals cueing a short FP_n (valid cue) than a long FP_n (invalid cue). Conversely and more relevant for our purposes, the FP_{n-1} influenced the CNV in a tonic fashion, independently of the cue. In particular, the amplitude of the ongoing CNV was lower throughout the FP_n with a long FP_{n-1} than with a short one. Notably, this pattern was observed *symmetrically* for both short and long current FPs_n. It is likely that sequential effects are usually compensated for during long FPs by the processes underlying the FP effect, thus accounting for their asymmetry. However, given the lack of a significant interaction between the sequential effects and the TMS site, further investigation is required to test the relationship between FP effect size and degree of symmetry of the sequential effects suggested by the pattern of the present results.

To the best of our knowledge, this is the first study in which an effect of the TBS parameters was demonstrated on behavioural variables (i.e., RTs) not directly linked to the measure of the motor cortex excitability, indicating its usefulness in cognitive neuroscience, as a feasible alternative to other kinds of off-line stimulation.

In conclusion, the present study demonstrated that the right DLPFC is a critical locus of the FP effect, as a reduction in this effect is obtained after TMS over that area. Moreover, the dissociation between the FP effect and the sequential effects produced by TMS of the right DLPFC, especially in experiment 2, suggests a dual-process account, according to which the two (usually interacting) effects are likely to be dissociable both functionally and anatomically.

Footnotes

Footnote 1. Strictly speaking, the FP is a continuous variable. In the current study, we decided to treat the FP as a categorical variable, using only three values of the FP (i.e., 0.5, 1 and 1.5 sec). This choice was aimed to allow comparison with the existing literature on the FP effect, where this variable has been almost always treated as categorical (see Niemi and Näätänen 1981, for a review), except for a few exceptions (e.g., Drazin, 1961).

Footnote 2. We chose this dependent variable as it directly estimates the direction of any change of the post-TMS RTs with respect to the baseline RTs (i.e., slowing or speeding). However, alternative ANOVAs were also conducted on the raw RTs, with FP_n, FP_{n-1}, TMS site (right and left DLPFC and right AG) and block (baseline and post-TMS block in experiment 1; baseline, first and second post-TMS blocks in experiment 2). These ANOVAs gave exactly the same results as those reported here, in both experiments. Specifically, the FP_n x TMS site x block interaction was significant [$F(4, 32)=3.4$, $p < .05$; $F(8, 64)=2.3$, $p < .05$, for the experiment 1 and 2, respectively], confirming the selective reduction of the FP effect after stimulation of the right DLPFC.

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Figure Captions

Figure 1. Hierarchical organization of experiment 1. See the Method section for details.

Figure 2. Brainsight localizations showing stimulation sites of the brain of a single participant, identified in co-registration with the TMS coil position. Panels A, B and C show the targeted sites in the right DLPFC, left DLPFC and right AG, respectively. In each panel, the regions in the crosshairs of the coronal, sagittal and axial views are based on the coordinates reported in Lewis and Miall (2003) (48, 42, 24 for the right DLPFC; the mirrored contralateral coordinates -48, 42 24 for the left DLPFC; 48 -45 48 for the right AG).

Figure 3. Mean RTs in experiment 1, as a function of FP on the current trial (x-axis), FP on the preceding trial (parameter), and experimental block (panels). Panels A, C and E refer to the baseline blocks before TMS on the right DLPFC, left DLPFC and right AG, respectively. Panels B, D and F refer to the blocks after TMS on the right DLPFC, left DLPFC and right AG, respectively.

Figure 4. Degree of change (in percentage) in mean RTs collected during the post-TMS block with respect to RTs collected during the pre-TMS baseline block (i.e., post-TMS RT/baseline RT x 100), in experiment 1. Data are plotted as a function of the stimulation site (x-axis) and of the current FP (parameter). Panels A, B and C refer to the blocks after TMS on the right DLPFC, left DLPFC, and right AG, respectively. * $p < .01$.

Figure 5. Mean RTs in experiment 2, as a function of FP on the current trial (x-axis), FP on the preceding trial (parameter) and experimental block (panels). Panels A, B and C refer to baseline, first and second blocks after TMS on the right DLPFC. Panels D, E and F refer to

baseline, first and second blocks after TMS on the left DLPFC. Panels G, H and I refer to baseline, first and second blocks after TMS on the right AG.

Figure 6. Degree of change (in percentage) in mean RTs collected during the two post-TMS blocks with respect to RTs collected during the pre-TMS baseline block, in experiment 2. Data are plotted as a function of the stimulation site (x-axis) and of the current FP (parameter). Upper and lower panels indicate results of the first and second post-TMS sessions, respectively. Panels A, B and C refer to the blocks after TMS on the right DLPFC, left DLPFC, and right AG, respectively. * $p < .05$.

Figure 1

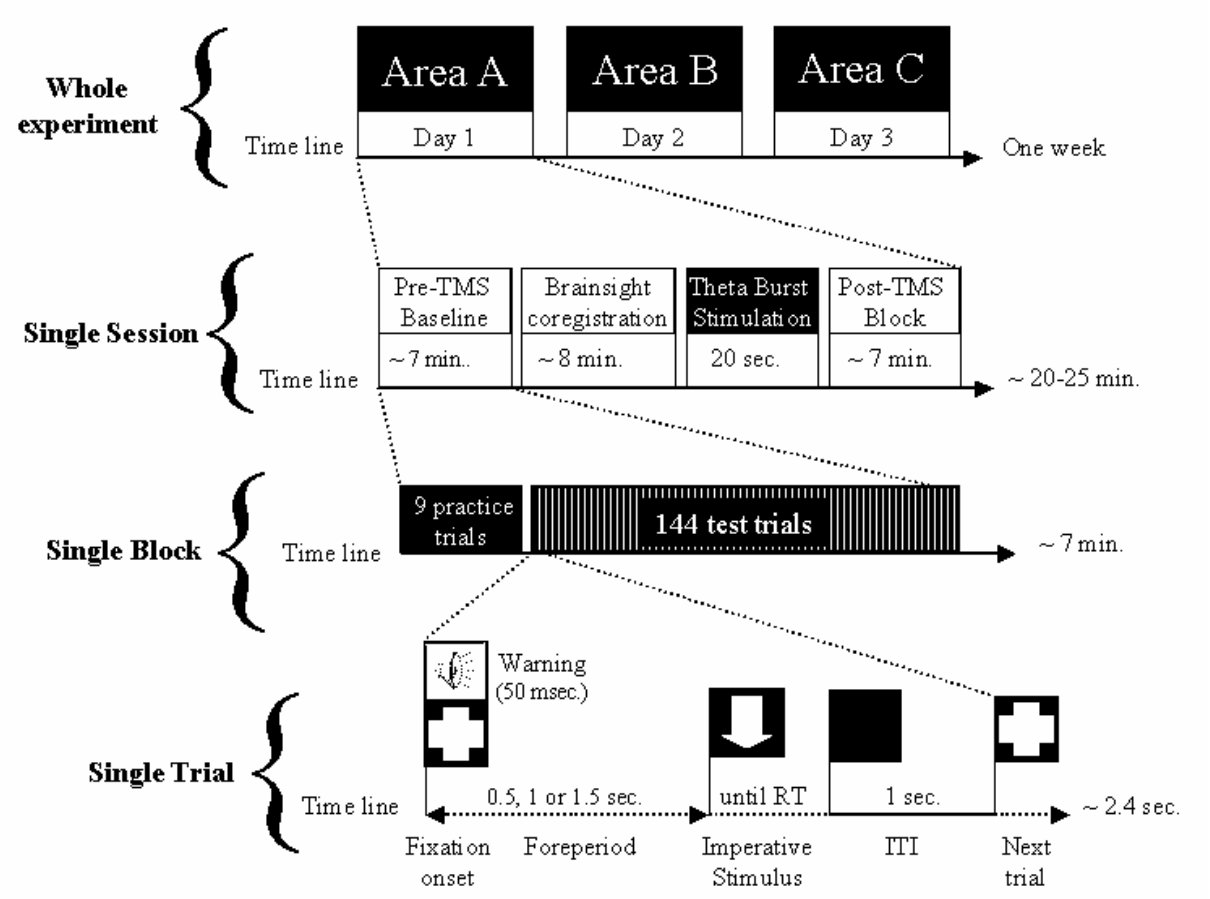

Whole experiment
Time line
Area A
Area B
Area C
Day 1
Day 2
Day 3
One week
Single Session
Time line
Pre-TMS Baseline
~7 min..
Brainsight coregistration
~8 min.
Theta Burst Stimulation
20 sec.
Post-TMS Block
~7 min.
~20-25 min.
Single Block
Time line
9 practice trials
144 test trials
~7 min.
Single Trial
Time line
Warning (50 msec.)
0.5, 1 or 1.5 sec.
until RT
1 sec.
~2.4 sec.
Fixation onset
Foreperiod
Imperative Stimulus
ITI
Next trial

Figure 2

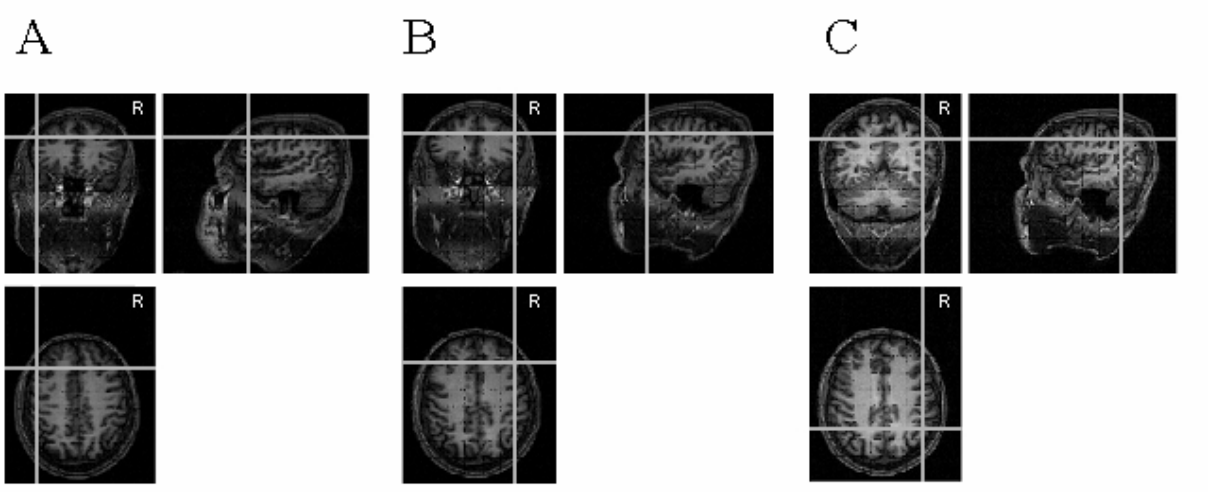


Figure 3

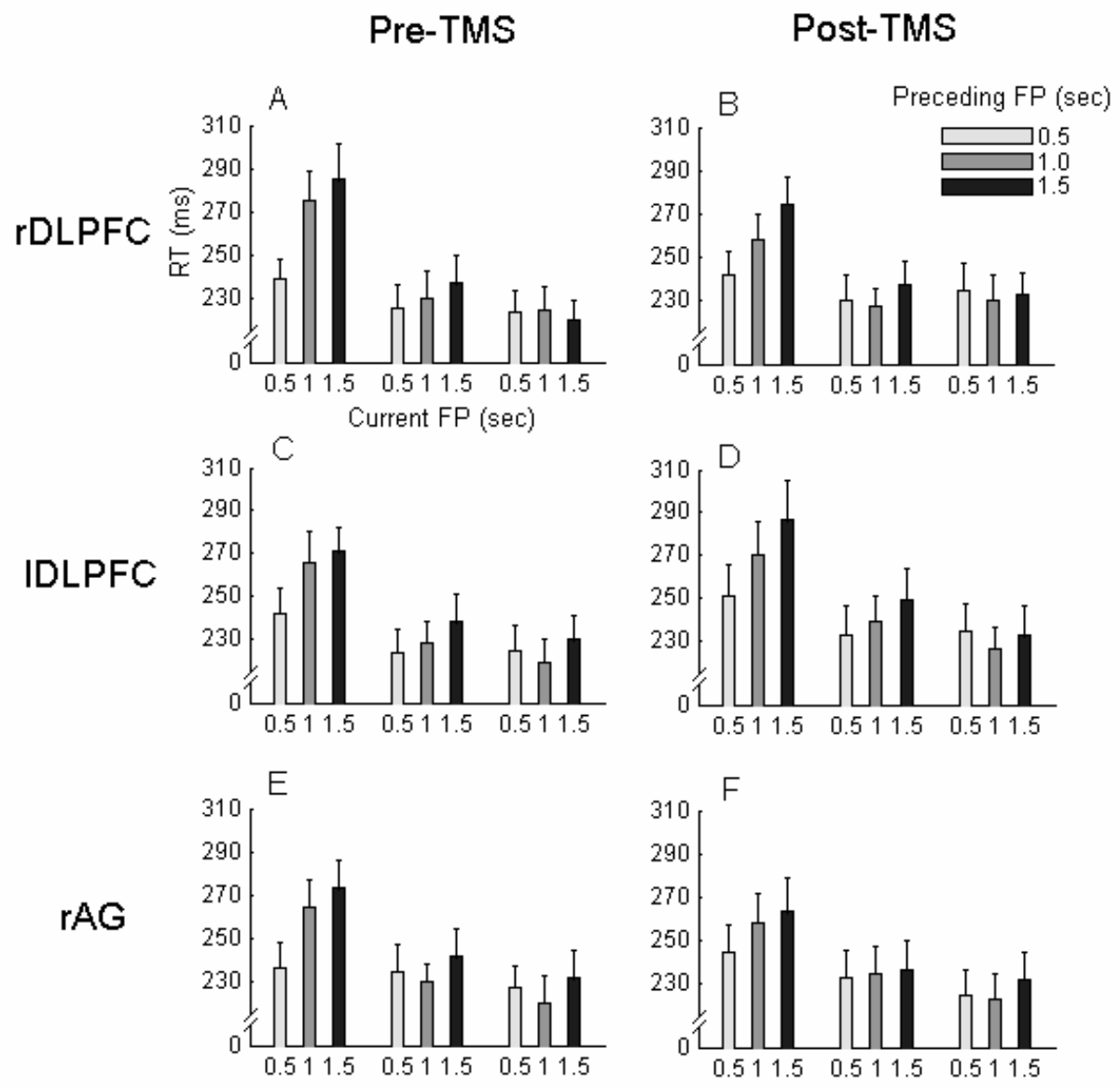
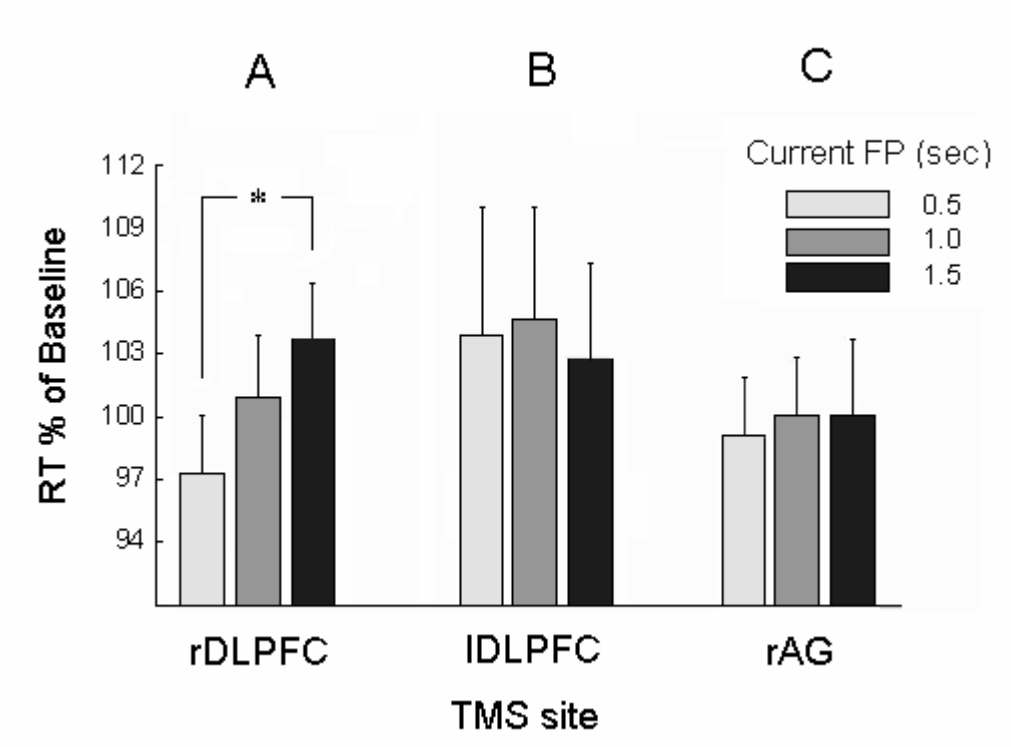

Pre-TMS
Post-TMS
rDLPFC
lDLPFC
rAG
A
B
C
D
E
F
RT (ms)
310
290
270
250
230
0
0.5 1 1.5 0.5 1 1.5 0.5 1 1.5
Current FP (sec)
Preceding FP (sec)
0.5
1.0
1.5

Figure 4


A
B
C
Current FP (sec)
0.5
1.0
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100
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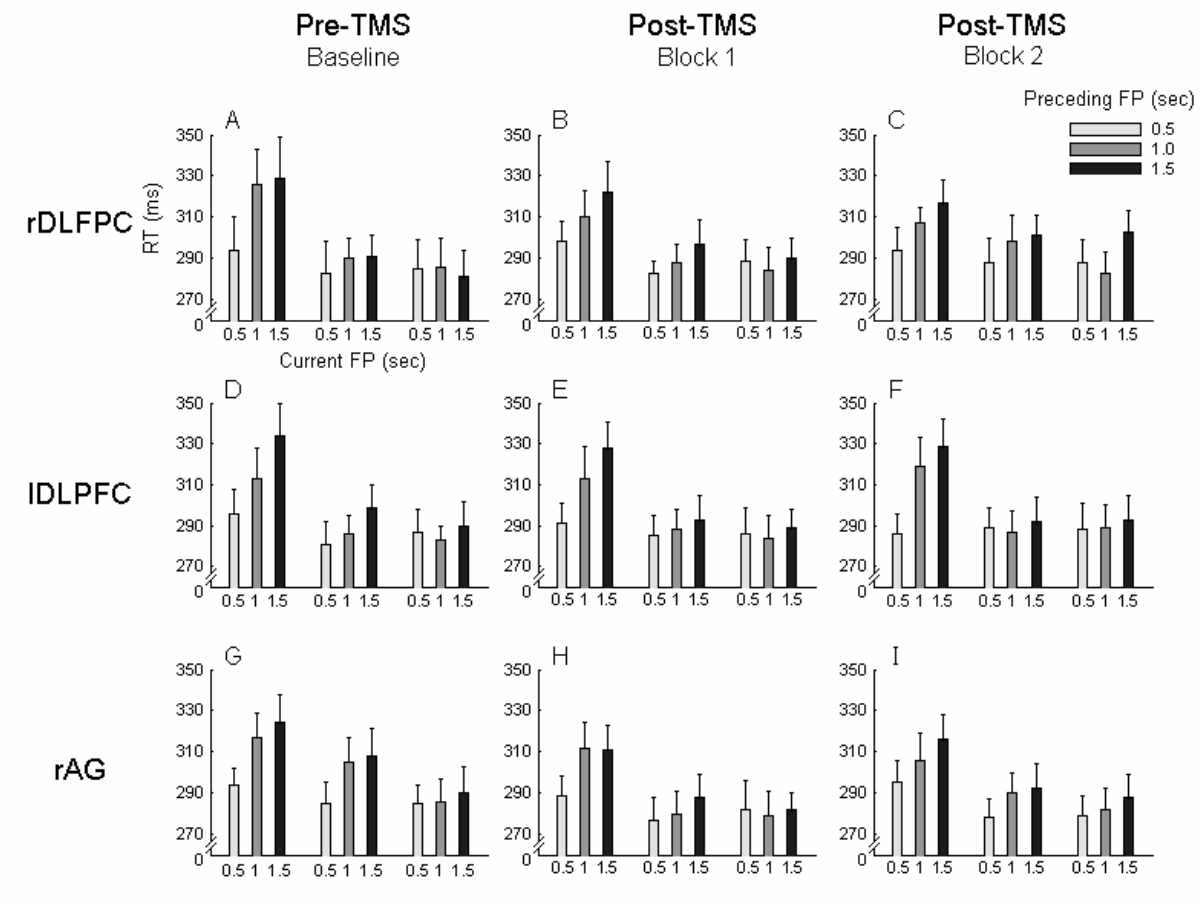
RT % of Baseline
rDLPFC
lDLPFC
rAG
TMS site

Figure 5


Pre-TMS
Baseline
Post-TMS
Block 1
Post-TMS
Block 2
Preceding FP (sec)
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1.0
1.5
rDLFPC
lDLPFC
rAG
RT (ms)
Current FP (sec)
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B
C
D
E
F
G
H
I
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310
290
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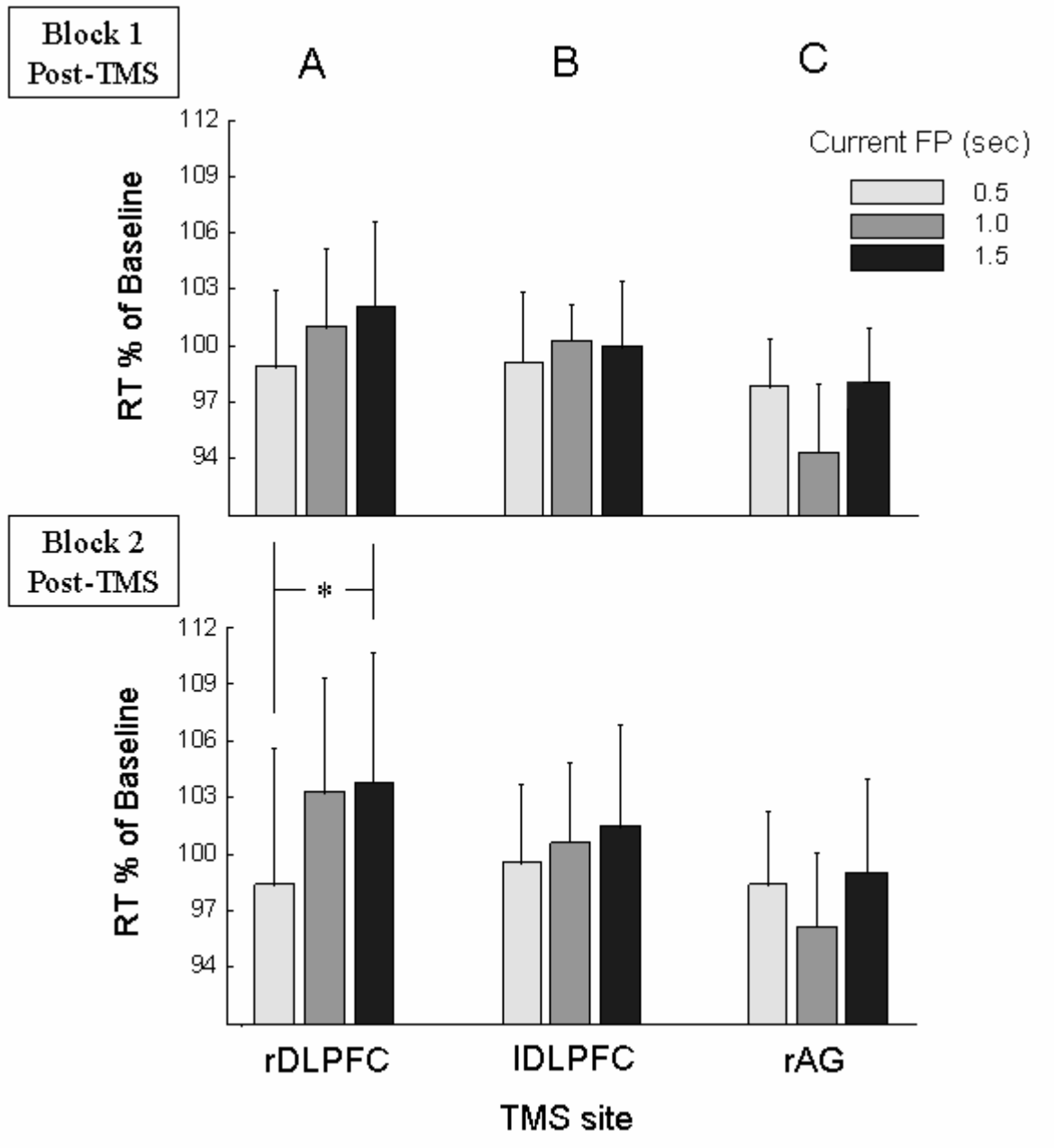
0
0.5 1 1.5

Figure 6


Block 1
Post-TMS
A
B
C
Current FP (sec)
0.5
1.0
1.5
RT % of Baseline
112
109
106
103
100
97
94
Block 2
Post-TMS
*
RT % of Baseline
112
109
106
103
100
97
94
rDLPFC
lDLPFC
rAG
TMS site