

Adaptations of Motor Neural Structures' Activity to Lapses in Attention

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Sustained attention is fundamental for cognition and when impaired, impacts negatively on important contemporary living skills. Degradation in sustained attention is characterized by the time-on-task (TOT) effect, which manifests as a gradual increase in reaction time (RT). The TOT effect is accompanied by changes in relative brain activity patterns in attention-related areas, most noticeably in the prefrontal cortex (PFC) and the right parietal areas. However, activity changes in task-relevant motor structures have not been confirmed to date. This article describes an investigation of such motor-related activity changes as measured with 1) the time course of corticospinal excitability (CSE) through single-pulse transcranial magnetic stimulation; and 2) the changes in activity of premotor (PMC), primary motor (M1), PFC, and right parietal areas by means of near-infrared spectroscopy, during a sustained attention RT task exhibiting the TOT effect. Our results corroborate established findings such as a significant increase ($P < 0.05$) in lateral prefrontal and right parietal areas activity after the emergence of the TOT effect but also reveal adaptations in the form of motor activity changes—in particular, a significant increase in CSE ($P < 0.01$) and in primary motor area (M1) activity ($P < 0.05$).

Keywords: motor preparation, NIRS, sustained attention, time-on-task, transcranial magnetic stimulation

Introduction

Sustained attention describes a fundamental aspect of cognitive processes vital for the successful execution of many activities of daily living, for example as in driving, or crossing a busy street. But attention resources are finite and a gradual decrease in attention across time—the so-called time-on-task (TOT) effect—usually arises from tasks requiring sustained attention. The TOT effect manifests behaviorally as an observable increase in reaction time (RT) over time and can therefore have serious consequences in terms of impaired performance in everyday tasks. For instance, attention deficits and fatigue have been linked with traffic accidents and work-related injuries (Czeisler et al. 2005). Other important areas where attention capacity has been identified as relevant include the clinical domain where patients suffering from attention deficit and hyperactivity disorder, can see their goal-directed behaviors disrupted by attentional lapses (Reimer et al. 2005). Investigating the neural bases of sustained attention is key to a deeper understanding of this vital cognitive property.

As noted by Fox et al. (2005), during the performance of attention-demanding tasks, certain attention-related areas routinely exhibit increased activity (e.g., lateral prefrontal cortex (PFC) and parts of the parietal cortex, Cabeza and Nyberg 2000), whereas others demonstrate decreases in activity (e.g., medial PFC, Gusnard and Raichle 2001). Further, Fox et al.

(2005) stressed that the more cognitively demanding the task, the higher the magnitude of these antagonistic patterns. In response to the TOT effect, marked increases (Paus et al. 1997; Fairclough et al. 2005; Weissman et al. 2006; Yarkoni et al. 2009) and decreases (Paus et al. 1997; Coull et al. 1998; Lim et al. 2010) in activity are evident in attention-related cortical areas. In one particularly relevant study, Weissman et al. (2006) investigated the trial-by-trial relationship between fMRI-measured brain activity and RT, and reported an increase in activity over the lateral PFC and parts of the right parietal area which was associated with the increase in RT. These authors concluded that the increase in activation observed after the occurrence of lapses in attention arose from increased demands on higher-order processing areas. The interpretation is that the longer attention is sustained, the higher the cognitive demand, and consequently the greater the activation in the lateral PFC and parts of the parietal cortex.

It is worth highlighting that neural activity changes associated with the TOT effect occurrence do not appear to be limited to known attention-related areas. Based on the aforementioned study by Weissman et al. (2006), albeit not highlighted by the authors, one can discern that the activity of the primary motor area (M1) contralateral to the limb involved in the RT also increases. However, apart from that study, no other research to date has focused explicitly on possible changes in the activity of motor structures once lapses in attention occur. This deficit impedes the creation of an integrated understanding of the adaptations of the nervous system to the TOT effect.

One means of investigating the activity of motor structures during RT tasks consists of using single-pulse transcranial magnetic stimulation (TMS) to probe the changes in corticospinal excitability (CSE) during movement preparation. During movement preparation, the CSE increases for the muscle group involved (Chen et al. 1998; McMillan et al. 2004; Mars et al. 2007; van Elswijk et al. 2008) and such neuronal activity changes characterize the motor preparation process (Rosenbaum 1980). To the best of our knowledge, motor preparation has been only investigated during phasic alertness studies and the evolution of premovement neuronal activity accompanying the TOT effect remains unknown. The increased evoked response over M1 associated with the increase in RT found by Weissman et al. (2006) could be related to an increase in the premovement excitability of the motor structures.

As a contribution towards a better understanding of the neural adaptations to the TOT effect, the study described here investigated the time course of the activity of motor structures through 2 complementary experiments. In the first experiment, the dynamics of CSE was assessed through measurement at 5 min intervals during a sustained attention RT task of 30 min duration. Single-pulse TMS was applied during the interstimuli intervals (ISI) as subjects prepared for the ensuing

stimulus. Through such an approach, we were able to focus on the neural correlates of motor preparation throughout the evolution of the TOT effect. In the second experiment, functional near-infrared spectroscopy (NIRS) was exploited to investigate the time course of the changes in activity of the cortical motor areas, PFC, and right parietal areas throughout the same sustained attention RT task. NIRS facilitates the investigation of cortical neural activity during hand movements in natural environmental settings which are comfortable and natural for subjects. This particular experiment allowed us to confirm previous results described in the literature regarding activity of attention-related areas as well as capturing any changes in the activity of relevant motor areas.

Materials and Methods

Two series of experiments were conducted to assess 1) the CSE (TMS experiment) and 2) the hemodynamic cortical changes (NIRS experiment) during 30 min of a sustained attention RT task. During both experiments, electromyographic (EMG) recordings and neuromuscular tests (NMT) were identically carried out. The study was split into 2 experiments because of the difficulties in investigating CSE by TMS concurrently with NIRS, for example, the placement of the NIRS optodes interferes physically with the placement of the coil necessitating an increase in the distance between the TMS coil and the scalp (i.e., beyond 20 mm). As it has been shown that the magnetic field generated by a TMS coil dies off very rapidly as a function of distance (Bohning et al. 1997), such an instrumentation arrangement is not satisfactory. To compound the difficulties, further it has been demonstrated that TMS can induce artifacts in NIRS measurements when performed over the same area (Näsi et al. 2011). The solution of 2 distinct experiments was therefore adopted to ensure independence of the TMS and NIRS measurements. The 2 experiments were conducted on 2 different groups of subjects to avoid the possibility of any task learning effects. Finally, a control experiment was performed on 4 subjects (recruited within the groups of the TMS and NIRS experiments) with single-pulse TMS and without a sustained attention RT task.

Participants

Fifteen right-handed male volunteers took part in the TMS experiment (aged 25.7 ± 3.6 years; height 1.79 ± 0.55 m; body weight 74.2 ± 7.2 kg) and 13 in the NIRS experiment (aged 29.0 ± 6.6 years; height 1.69 ± 0.34 m; body weight 80.6 ± 3.4 kg). Student's *t*-test for groups performed on the age, height, and body weight revealed no significant difference in these parameters between the groups of the NIRS and TMS experiments ($P=0.36$; $P=0.71$; $P=0.33$; respectively). All subjects were right-handed according to the Edinburgh Questionnaire (Oldfield 1971). No subject had any sign of neurological, respiratory, and cardiovascular disease or medication, which might affect brain and muscle functions. Neither had any subject epileptic antecedents which would have precluded the use of the TMS technique. Each subject provided written informed consent prior to participation in the study. All procedures were approved by the local ethics committee (CPP Sud-Méditerranée II, number 2010-11-05) and complied with the Declaration of Helsinki for human experimentation.

Experimental Design

Both experiments were conducted in a quiet and dimly lit room. Each subject performed the entire protocol once. The subjects were asked to sit at a table on which a stimulus light (white) source was positioned at a distance of 1 m from the subject's eyes (Fig. 1). A computer screen was positioned just behind and above the light source to provide visual feedback of the force generated during certain phases of the protocol. The subjects wore a neck brace to reduce head movements and the head was fixed against a headrest by means of straps. The left forearm of each subject was rested upon the surface of the table. The dominant hand (i.e., right hand for these subjects) was held in a neutral position

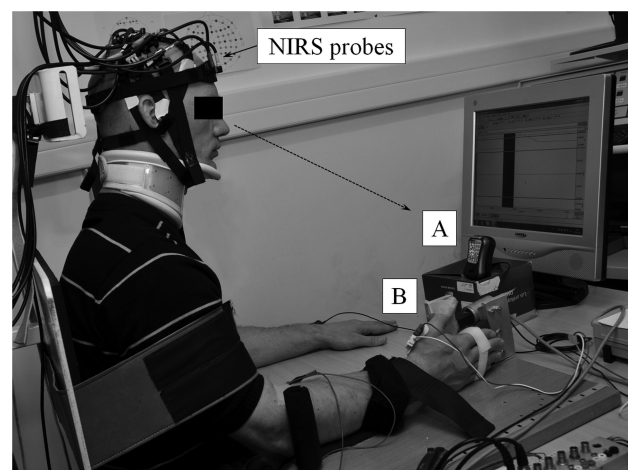


Figure 1. The experimental setup during the NIRS experiment. (a) Light source evoking the visual target stimuli during the sustained attention RT task. From the beginning of the task, subjects had to attend and prepare for the upcoming stimulus when the lighting source was off (i.e., during interstimuli intervals). Subjects were instructed that when a flash occurred they should generate a thumb abduction as quickly as possible. (b) Dynamometer allowing the measurement of the thumb abduction movements (i.e., the motor responses). EMG electrodes can be distinguished on the belly of APB muscle. The screen positioned just behind the light source was turned off during the task and the resting state periods and turned on during the periods of the protocol requiring a visual feedback of the force production (i.e., during the neuromuscular tests and the warming-up phase).

in the sagittal plane and fixed with straps to prevent extraneous movements during contractions. The angle of the elbow was set to 110° (with 180° corresponding to full elbow extension). The thumb was fixed against a dynamometer allowing direct measurement of abduction force (Captels, Saint-Mathieu-de-Trévières, France). The angles between the distal and the intermediate phalanx, and between the intermediate phalanx and the metacarpus were set to 180° and 70° , respectively. This thumb position allowed measurement of the highest EMG activity of the abductor pollicis brevis (APB) muscle in response to TMS and NMT. The arrangement is illustrated in Figure 1.

Experimental Protocol

First, a standard warm-up phase was performed consisting of 20 static submaximal contractions of the right APB (i.e., through a thumb abduction task) in an intermittent mode. The level of force was maintained for 5 s followed by 5 s of recovery and was gradually increased after the 10th contraction. Visual feedback of the level of force generated was presented (a red trace) in real time on the screen in front of the subjects (see Fig. 1). Subjects were asked to match the red trace on the computer screen by modulating their motor activity. Then, the subjects produced 3 maximal voluntary contractions (MVC) of 5 s duration followed by 60 s of passive recovery. Afterward, a simple visual RT task was performed of 1 min duration in order to familiarize the subjects with the paradigm. The task onset signal consisted of a 150-ms flash stimulus delivered using the light source (i.e., photodiode arrays consisting of a few dozen emitters). A randomly varying ISI was set with a range of between 2 and 15 s. The motor response required of the subject was thumb abduction and this had to be performed as quickly as possible in response to the visual stimulus. In this sense, the task exploited in our protocol closely replicated the characteristics of the psychomotor vigilance test developed by Dinges et al. (1997). We selected a simple RT task for 3 main reasons. First, simple RT tasks have been shown to be highly sensitive to changes in attention (Dinges et al. 1997; Lim et al. 2010). Second, during simple RT tasks, the stimulus saliency remains constant throughout the task. Therefore, the maintenance of optimal performance is mediated only through top-down processes without any stimulus-driven increase in the level of attention. Third, the absence of distracting stimuli allows the motor

response to be fully prepared without the involvement of any inhibitory process (i.e., in contrast to RT tasks which involve choice or recognition components). Consequently, the simple RT task exploited here allowed investigation of the neural substrates of the motor preparation process without any influence from the inhibition of inappropriate motor responses during the ISIs. The thumb abduction movement was chosen in this study as it facilitates easier EMG measurement over the APB muscle in response to single-pulse TMS (Chen et al. 1998). This muscle, investigated during the TMS experiment, was also the main muscle involved in the motor response following the visual stimulus. Next, we determined the intensity of median nerve stimulation required to measure the maximal amplitude of the M-wave (I_M) and of the superimposed H-reflex (I_{Hsup} ; for more details, see below) and began the NMT. This consisted of 3 single stimuli at I_M separated by 10 s intervals, and 3 single stimuli at I_{Hsup} . The contractions required to obtain the Hsup were performed at 10% MVC and separated by 20 s intervals. The NMT time course is shown in Figure 2A, and was realized before (pretask NMT) and after (post-task NMT) the sustained attention RT task. Monitoring these neuromuscular variables (i.e., H-reflex and M-wave) allowed us to assess whether or not the repetition of thumb abduction in the protocol induced fatigue at the spinal and muscle levels (Gandevia 2001). Immediately after the experiment, the rating of perceived exertion (RPE) was evaluated by means of the Borg scale (from 6 to 20; Borg 1970).

TMS Experiment

After the pretask NMT, a number of TMS pulses (in this case, 4 pulses) at a level of intensity that elicited the largest motor evoked potential (MEP) amplitude and reproducibility (I_{MEP} ; for more details describing how this level was determined, see below) were delivered at rest and also during voluntary contractions at 10% MVC. Next, a sustained attention RT task of 32 min was performed with the same characteristics as the 1-min familiarization task. The average number of stimuli presented to the subjects over course of the task was 275 stimuli. Four TMS pulses at I_{MEP} were realized during the 2nd minute (post 1) of the task and every 5 min thereafter (post 5, post 10, post 15, post 20, post 25, post 30) with variable interstimulation periods. The inter-TMS pulses intervals ranged from 5 to 15 s. The stimulation phases were delivered during the motor preparation period (i.e., during ISIs), but never during motor execution. The task duration was set to 32 min in order to accommodate a measurement of CSE just beyond the 30-min period. Just after the RT task, TMS pulses at I_{MEP} were delivered both at rest and during voluntary contractions at 10% MVC (post-task TMS). These post-task TMS pulses allowed us to investigate the changes in CSE once the RT task was complete. Specifically, we assumed that if the expected change in MEP amplitude occurred during the task, a return of this variable to the baseline (i.e., pretask) value following the task would definitively highlight a link between the act of performing the sustained attention task and the increase in MEP amplitude. It was

followed by the post-task NMT, the production of one MVC, and the estimation of RPE. The NMT was performed in all subjects during the TMS experiment.

A control experiment was performed on 4 subjects to ensure that there was no effect from the repetition of TMS pulses on the MEP amplitude. It consisted of the delivery of 4 TMS pulses at I_{MEP} (equivalent to the pretask TMS), followed by 4 TMS pulses 2 min later and every 5 min thereafter during the following 32 min (equivalent to the post 1, post 5, post 10, post 15, post 20, post 25, and post 30 TMS) and 4 TMS pulses just after 32 min (equivalent to the post-task TMS). During this control experiment, the subjects were instructed to sit relaxed, with neither visual stimulus presentation, nor motor responses required.

NIRS Experiment

After the pretask NMT, the subjects were instructed to rest for 2 min in order to stabilize the NIRS signals. This was followed by a sustained attention task of 32 min whose characteristics were the same as those during the 1-min familiarization task. After the sustained attention RT task, a 2-min resting period followed. This was in turn followed by the post-task NMT, the production of one MVC, and the estimation of RPE. The NMT was performed in 10 of 13 subjects in the NIRS experiment. Over the course of the experiment, specific NIRS events markers were generated through the NIRS software (V6.0, Artinis, The Netherlands) in order to demarcate the periods of interest (i.e., baseline and task). The time course of NIRS and TMS protocols are displayed in Figure 2B.

Measurements

Electromyographic Recording

The EMG signals of the right APB muscle were recorded using bipolar, Ag/AgCl, square surface electrodes with a 9-mm diameter (Contrôle Graphique Médical, Brie-Compte-Robert, France). The skin was shaved, abraded, and washed with emery paper and cleaned with 70° alcohol in order to obtain low impedance between the 2 bipolar electrodes (<5 k Ω). The electrodes were positioned on the belly of APB muscle. The interelectrode distance was 20 mm. The reference electrode was placed on the styloid process of the left ulna. The EMG cables were strapped to the table to prevent movement artifacts. The EMG signals were amplified ($\times 1000$), digitized at 2048 samples per second and synchronized with the force/motor responses and stimuli signals using the Biopac MP100 data acquisition system (Biopac System, Inc., Santa Barbara, CA, USA).

Near-Infrared Spectroscopy Recording

Functional NIRS is a versatile neuroimaging tool with an increasing acceptance in the neuroimaging community (Cui et al. 2011; Derosi re et al. 2013). Specifically, NIRS allows measurement in less constrained settings than those afforded by neuroimaging technologies such as

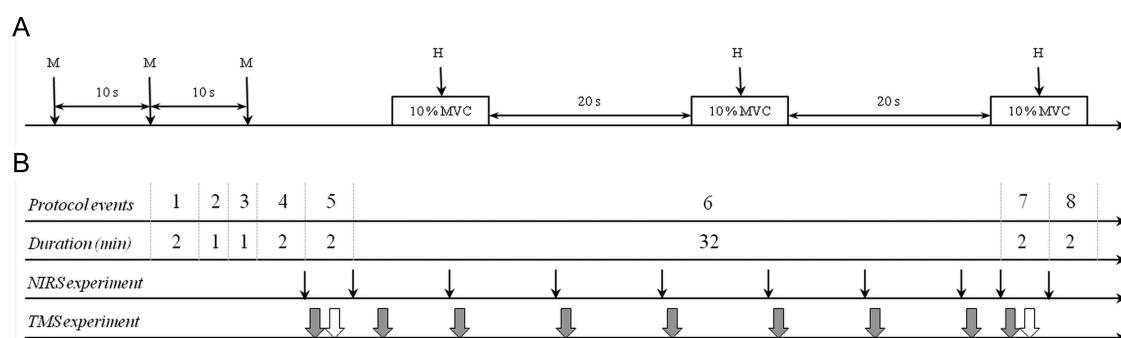


Figure 2. (A) Neuromuscular tests (NMT). M and H represent the neural stimulation pulses performed at the intensity generating the M-wave and the superimposed H-reflex responses, respectively. MVC, maximal voluntary contraction. (B) Time course of NIRS and TMS protocols. Protocol events are 1: Warming-up. 2: Resting period. 3: Familiarization through 1 min of sustained attention. 4: pretask NMT. 5: NIRS experiment = pretask resting period; TMS experiment = pretask TMS. 6: Sustained attention task for 32 min. 7: NIRS experiment = post-task resting period; TMS experiment = post-task TMS. 8: post-task NMT. The thin black arrows in NIRS experiments represent the NIRS events, delineating the resting state periods and the task and each 5 min of the task. In TMS experiment, the thick gray arrows represent 4 TMS pulses without any contraction and the thick white arrows represent 4 TMS superimposed pulses (with voluntary contractions at 10% MVC).

MRI, for example, in this case a sitting position, which is less susceptible to drowsiness than supine (Kräuchi et al. 1997). Further, NIRS allows subjects to perform tasks free from disturbance from scanner noise (in the case of MRI) and represents therefore a suitable technique for the investigation of focused attention. Functional NIRS utilizes, as fMRI, the tight coupling between neuronal activity and regional cerebral blood flow (Villringer and Dirnagl 1995) to measure regional hemodynamic concentration changes in oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb) in the brain. By placing a pair of probes—consisting of an emitter of near-infrared light and a receptor—the relative local changes in the absorption and scattering of photons can be measured. These changes allow one to infer the relative local changes in hemoglobin state. Simulations have demonstrated (Haessinger et al. 2011) that the mean penetration depth of the photons for an interoptode distance of 3.5 cm in adults is 23.6 ± 0.7 mm and it follows a banana-shaped pathway. For more details about the basic principles of NIRS, please refer to the recent review of Ferrari and Quaresima (2012).

NIRS measurements were performed using a continuous wave multichannel system (Oxymon Mk III, Artinis, The Netherlands). The sampling rate was set to 10 samples per second. This particular device measured changes in optical density at 2 different wavelengths in the near-infrared range (nominal wavelengths 763 and 855 nm) and processed these to produce the corresponding changes in concentration levels of $[O_2Hb]$ and $[HHb]$. A subject-specific differential pathlength factor was used for this conversion based on the age of each subject (Duncan et al. 1996) to yield more accurate measurement of the concentration changes in $[O_2Hb]$ and $[HHb]$ in terms of μM units (Delpy et al. 1988). The interoptode distance for each channel was set at 3.5 cm. Nine channels (each consisting of a 2-wavelength source and detector) were used—3 were positioned over the frontopolar part of the left, the right, and the medial PFC (IPFC, rPFC, and mPFC, respectively), 1 over the left premotor cortex (IPMC), 1 over the left primary motor area (IM1), and 4 over the right parietal area. The optodes were positioned according to the modified international EEG 10-10 system (American Electroencephalographic Society 1994) and mounted on a custom-made cap fixed by several bands to the head of the subject. According to the EEG 10-10 system, the locations of the center of the channels over the IPFC, rPFC, mPFC, IPMC, IM1 corresponded to the Fp1, Fp2, Fpz, FC3, and C3 points, respectively. In separate independent studies (Anwar et al. 2013; Muthalib et al. 2013), we confirmed these NIRS channel positions as being over IM1, IPMC, and PFC from activation maps of fMRI and using fiducial markers. The center of the 4 channels set in a square template over the right parietal area corresponded to the P6 point. During the placement of the probes, the Oxysoft software (V6.0, Artinis, The Netherlands) displayed real time measures of the signal quality for each NIRS channel based on the light source power level and the receiver gain. Once an acceptable signal-to-noise ratio was obtained, a zero baseline was set and the protocol executed.

Stimulation Recordings

Median nerve stimulation. Muscular and spinal excitability was evaluated by the M-wave and the superimposed H-reflex (Hsup), respectively. These potentials were obtained by stimulation of the median nerve by means of a high-voltage, constant-current stimulator (DS7AH, Digitimer Ltd., Hertfordshire, UK). Rectangular monophasic pulses of 500 μs were used. The cathode and the anode (Ag/AgCl electrodes) were placed over the pathway of the median nerve in the proximal and anterior part of the forearm. The first step consisted of the determination of the intensity of stimulation for each subject. To do so, we generated recruitment curves at the beginning of the experiment. We increased the current intensity by 5 mA increments every 10 s, to identify the individual stimulation intensity at which no further increase in the amplitude of the APB muscle potential (M-wave) was observed (I_M). Afterward, subjects were asked to perform a voluntary contraction at 10% MVC, during which pulses at weaker intensity (i.e., less than I_M) were delivered eliciting Hsup. The muscle contractions were separated by 20 s of passive recovery.

Intensity was decreased by 5 mA, until the maximum amplitude of the Hsup (I_{Hsup}) was obtained.

Transcranial magnetic stimulation. Single TMS pulses of 1-ms duration were delivered using a Magstim 200 (Magstim, Whitland, UK) via a figure-of-eight coil (double 70 mm-diameter coil, maximum output intensity 2.2 T). The coil was positioned over the right-hand cortical representation of left motor cortex according to the C3 point of the 10-10 EEG system. The position was then adjusted in small amounts by moving the coil in the sagittal and coronal planes until the largest MEP was elicited in the right APB at 50% of the maximal stimulator power output. The coil was held in position by straps surrounding a metallic spindle mounted on a mechanical arm with 6 degrees of freedom. Markers were positioned both on the subjects and the coil to precisely locate the position of the coil. An investigator remained during the experiment behind the subject to ensure that the coil did not move (as could be assessed via relative movement between the markers on the subject and the coil). To determine the TMS intensity of stimulation for each subject, individual recruitment curves were derived by gradually increasing the TMS intensity in steps of 10% of the maximal stimulator power output. This process began at 50% of the stimulator output and executed 4 stimulations per intensity with an ISI of 10 s, and finished at 100% of the maximal stimulator power output. The stimulation intensity that elicited the largest MEP amplitude and reproducibility (I_{MEP}) was selected for subsequent measurement.

Data Analysis

Reaction Time

The RT data was processed through the Acknowledge software associated with the Biopac system (Acknowledge 3.8.1, Biopac Systems, Santa Barbara, CA, USA). The RT was measured as the time between the flash stimulus (target stimulus) and the beginning of force production. The first 5 RTs of the task and the last 5 RTs of each block (1 block = 5 min) of the 32-min sustained attention task were then measured. Next, averages of the 5 RTs for each part of the protocol were obtained resulting in the mean RT at intervals corresponding to the 1st, 4th, 9th, 14th, 19th, 24th, and 29th minute of the task. This avoids any confounding effect of the TMS pulses which took place at the beginning of the 2nd, 5th, 10th, 15th, 20th, 25th, and 30th minute of the task.

NMT

NMT data were also processed through the Acknowledge software. The peak-to-peak amplitudes of the M-wave and Hsup were calculated for each trial and then averaged for the pre- and post-task NMT. The Hsup/M ratios were also calculated to ensure that there was no influence of peripheral changes on the spinal excitability parameters. During pre- and post-task MVCs, the highest plateau of force in excess of 500 ms was considered as the maximal voluntary force.

TMS

The peak-to-peak amplitudes of the MEP at rest and during the sustained attention task were calculated for each TMS pulse. In order to prevent contamination of the MEP measurements by background EMG activity, trials with background EMG activity >100 μV in the 200-ms window preceding the TMS artifact were excluded from the MEP analysis (Duque and Ivry 2009). The peak-to-peak amplitudes of the MEP were then averaged according to the protocol as follows: pretask, 1, 5, 10, 15, 20, 25, 30 min, and post-task. The percentages of the MEP amplitude during and after the task were calculated with reference to the pretask MEP amplitude. The MEP/M and MEP/Hsup ratios were calculated with respect to the pre- and post-task MEP to ensure that there was no influence of peripheral and spinal changes, respectively, on the central parameters. To do so, the pre- and post-task NMT were used to normalize the pre- and post-task MEP, respectively. The peak-to-peak amplitude of the MEP was also calculated during the contractions at 10% MVC and normalized on M (MEP_{sup}/M) and Hsup ($MEP_{sup}/Hsup$) amplitude at the same level of exerted force. The silent period

(SP) duration was measured for pre- and post-task TMS as the time between the pulse occurrence and the return of uninterrupted tonic EMG activity during the contractions at 10% MVC. Similarly, for the MEP amplitude, this calculation was realized for each TMS pulse and then averaged for pre- and post-task TMS.

NIRS

As is common for the modality (see Yamanaka et al. 2010), we focused on $[O_2Hb]$ as the variable of interest to determine changes in cortical activity. Changes in $[O_2Hb]$ have been recognized to better reflect cortical activation than $[HHb]$ due to its superior contrast-to-noise ratio (Strangman et al. 2002). Dedicated NIRS software was used to analyze the $[O_2Hb]$ signals acquired. The raw data were processed offline using the Oxysoft analysis program (V6.0, Artinis, The Netherlands) associated with the multichannel NIRS Oxymon Mk III system. The first step consisted of a preprocessing visual analysis as proposed in Minagawa-Kawai et al. (2011). The aim of this step is to remove channels where large movement artifacts had occurred or where signal-to-noise ratio was poor because of the presence of hair underneath the optodes. Then, the raw NIRS data were low-pass filtered using a cut-off frequency of 0.1 Hz in order to remove the heart rate and respiratory components (Huppert et al. 2009). From the resulting individual signals, the $[O_2Hb]$ values were averaged over the 1st minute of the pretask baseline, the 2nd, 5th, 10th, 15th, 20th, 25th, and 30th minutes of the task. Then, the average of the 1st minute of the pretask baseline was subtracted from the averages of the other periods resulting in a differential in hemoglobin concentrations ($\Delta[O_2Hb]$) at 1, 5, 10, 15, 20, 25, and 30 min of task. These calculations were executed for the 9 channels. The changes in $\Delta[O_2Hb]$ for the 4 channels over the right parietal area were averaged together resulting in an overall right parietal response. The use of the average from these 4 channels was considered suitable given the lack of significant differences in $\Delta[O_2Hb]$ between these measurements over the right parietal area ($F(3, 18) = 0.19$, $P = 0.91$).

Statistical Analysis

Statistica software (version 7.0, Statsoft, Oklahoma, USA) was used for all analyses. All data were examined for normality and homogeneity of variance using Skewness, Kurtosis, and Brown-Forsythe tests. A 1-way repeated-measure ANOVA was used to test for any significant effect of time (1, 9, 14, 19, 24, and 29 min) on the changes in RT with a categorical factor (experiment, NIRS vs. TMS) to test for any divergence between the TOT effect on the RT during both experiments. Also, a 1-way repeated-measures ANOVA was used to test for any significant effect of time (1, 5, 10, 15, 20, 25, and 30 min) on the changes in $\Delta[O_2Hb]$ over the IPFC, rPFC, mPFC, lPMC, lM1, and right parietal areas. When appropriate, the Fisher's LSD post hoc test was used to detect paired differences. Due to multiple comparisons, we applied a strict 0.008 alpha level of significance (after Bonferroni correction) in the ANOVA performed on the NIRS data. Nonparametric Friedman ANOVA was performed to test for the significant effect of time (pretask, 1, 5, 10, 15, 20, 25, 30 min, and post-task) on the changes in MEP amplitude during the TMS experiment. The same Friedman ANOVA test was performed to test for the significant effect of time on the changes in MEP amplitude during the control experiment as well. When appropriate, the Conover's post hoc test was used to detect paired differences. Student's *t*-test was used for paired samples to test for pretask to post-task differences in M, Hsup/M, MEPsup/M, MEP/M, MEPsup/Hsup, SP duration, and MVC. Student's *t*-test was also used for groups to compare the RPE measured after the NIRS and TMS experiments. The significance level was set at $P < 0.05$. Data are presented mean $\pm$ standard deviation (SD).

Results

RT and RPE data

As expected, the results did not show any significant difference between groups (i.e., from NIRS and TMS experiments) with

respect to the evolution of RT over time ($F(6, 144) = 0.54$, $P = 0.77$) and the TOT effect in both groups ($F(6, 144) = 18.42$, $P < 0.001$). The RT results demonstrate that the TOT effect occurred (according to significance measures) after 9 min over the sustained attention task. These results are presented in Figure 3. The *t*-test showed that the RPE values were not significantly different between the NIRS and TMS experiments ($t = 0.25$; $P = 0.83$). The RPE score after the NIRS and TMS experiments were 14.58 ± 1.73 and 13.71 ± 1.27 , respectively.

Pre- and Post-task NMT

The Student's *t*-test for paired samples showed no significant difference between pre- and post-task M-wave ($t = 0.03$, $P = 0.98$), Hsup/M ($t = 0.79$, $P = 0.43$), and MVC ($t = 0.87$, $P = 0.39$). All NMT results are presented in Table 1.

NIRS

All precautions were taken during the installation of the NIRS headset in order to pull hair away from the probes location. However, the data obtained from some subjects for the channels positioned over hair-covered areas showed a low signal-to-noise ratio because of the paucity of near-infrared light detected. Thus, 21.2% of the NIRS signals were removed from the analysis.

A significant increase in $\Delta[O_2Hb]$ over time was observed over the IPFC ($F(6, 72) = 5.89$, $P < 0.001$), the rPFC ($F(6, 72) = 2.99$, $P < 0.01$), the lM1 ($F(6, 48) = 3.35$, $P < 0.05$), and the right parietal area ($F(6, 36) = 9.15$, $P < 0.001$). A significant

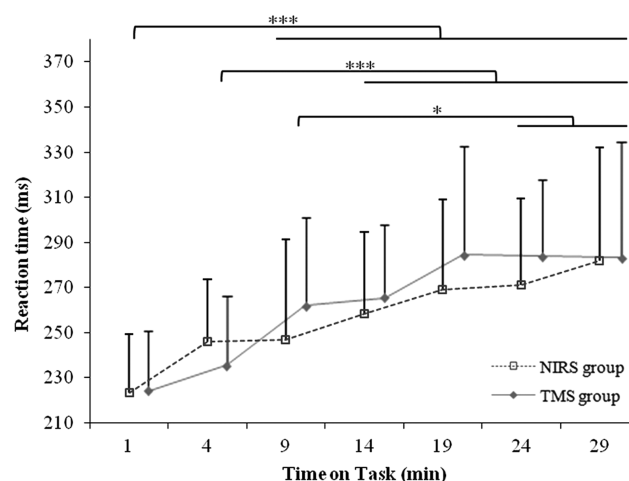


Figure 3. Evolution of reaction time over time during a sustained attention RT task of 30 min. Significant increase in RT occurred after 9 min of task compared with RT values of the first minute of task. *** $P < .001$; * $P < 0.05$. Vertical bars represent SD.

Table 1

Comparison of pre- and post-task NMT and TMS variables

Variables	Pretask	Post-task	<i>P</i> -value
MVC (N) ($n = 27$)	73.79 $\pm$ 44.9	62.4 $\pm$ 38.1	0.39
M amplitude (mV) ($n = 22$)	8.52 $\pm$ 3.29	8.49 $\pm$ 3.5	0.98
Hsup/M (mV) ($n = 19$)	0.19 $\pm$ 0.09	0.22 $\pm$ 0.1	0.43
MEPsup/M (mV) ($n = 13$)	0.65 $\pm$ 0.23	0.71 $\pm$ 0.29	0.57
MEPsup/Hsup (mV) ($n = 12$)	3.61 $\pm$ 2.19	3.67 $\pm$ 2.03	0.95
MEP/M (mV) ($n = 13$)	0.20 $\pm$ 0.15	0.24 $\pm$ 0.18	0.53
SP duration (ms) ($n = 13$)	216.87 $\pm$ 41.29	218.3 $\pm$ 43.76	0.93

Results represent mean $\pm$ SD. The *P*-values are these of the *t*-tests.

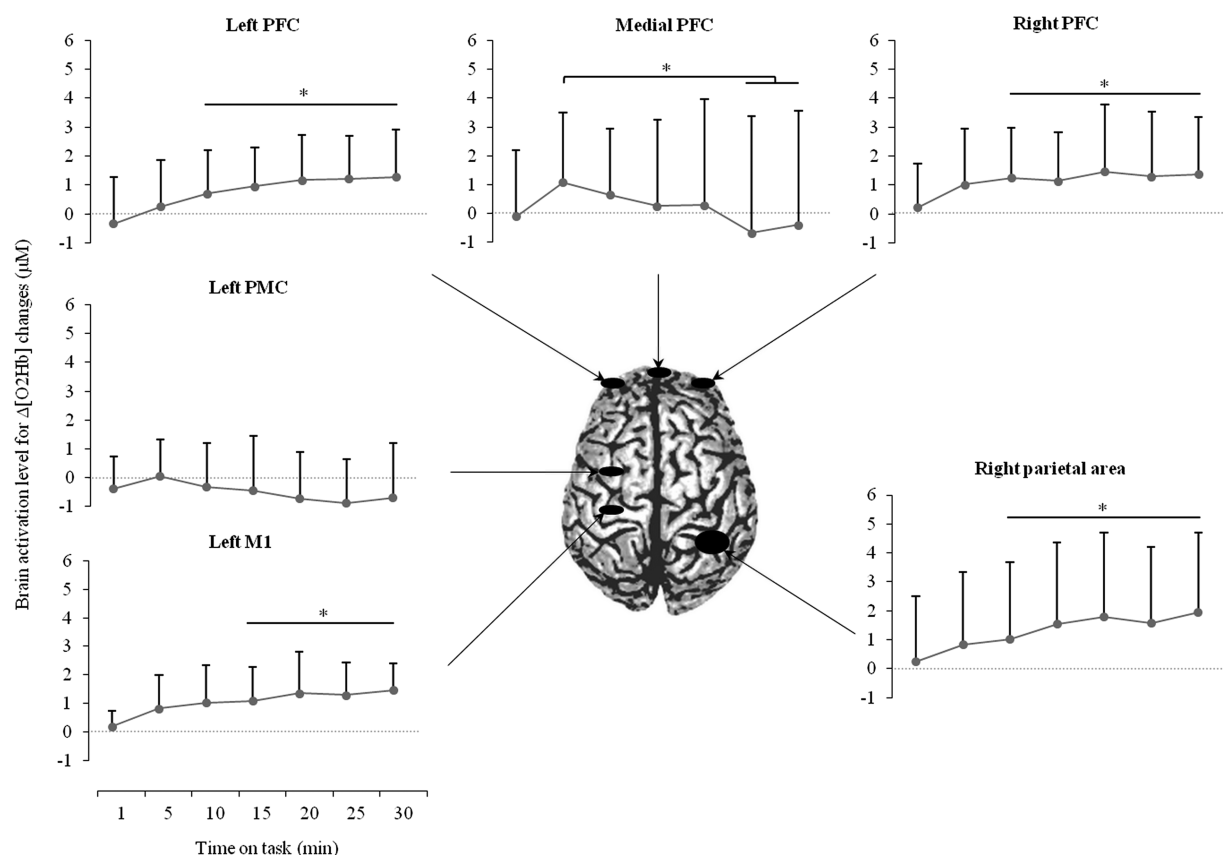


Figure 4. Evolution of NIRS signals over time during a sustained attention RT task of 30 min. $*P < 0.05$ after Bonferroni correction. Gray traces represent $\Delta[\text{O}_2\text{Hb}]$ changes. Significant changes are the results of post hoc tests and horizontal bars represent comparisons with cortical activation after 1 min of task over the respective area (except for the mPFC where the significant changes are compared with the cortical activation after 5 min of task). Black circles represent the cortical areas investigated by the NIRS probes. Vertical bars represent SD.

decrease in $\Delta[\text{O}_2\text{Hb}]$ over time was observed over the mPFC ($F(6, 60) = 2.62$, $P < 0.05$). No significant change in $\Delta[\text{O}_2\text{Hb}]$ was found over the IPMC ($F(6, 54) = 1.35$, $P = 0.25$). Detailed post hoc tests results of NIRS data are reported in Figure 4.

TMS

A significant increase in MEP amplitude was observed over time for the TMS group ($F(13, 8) = 38.31$, $P < 0.001$) but not for the control subjects ($F(4, 8) = 5.33$, $P = 0.72$). These results are presented in Figure 5. The Student's t -tests for paired samples showed no significant difference between the pretask and the post-task in MEPsup/M ($t = 0.58$, $P = 0.57$), MEP/M ($t = 0.64$, $P = 0.53$), MEPsup/Hsup ($t = 0.07$, $P = 0.95$), and SP duration ($t = 0.08$, $P = 0.93$). These results are presented in Table 1.

Discussion

The aim of this study was to highlight how the activity of motor structures, in concert with attention-related cortical areas, adapts to the occurrence of the TOT effect. Our experimental design produced a TOT effect after, on average, 9 min of sustained attention as revealed by the significant increases in RT ($P < 0.001$). Our measurements and analysis demonstrate a significant increase ($P < 0.05$) in NIRS-measured lateral PFC (right and left) and right parietal areas activity concomitant

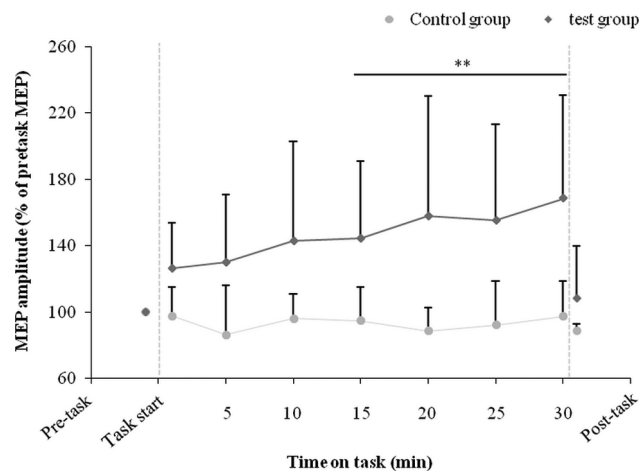


Figure 5. Evolution of the largest motor evoked potential (MEP) amplitude over time during a sustained attention RT task of 30 min (experimental group) and at rest (control group). $**P < 0.01$. Significant changes are the results of post hoc tests and horizontal bars represent comparisons with pre- and post-task MEP amplitude values. Vertical gray dotted lines delimit the beginning and the end of the sustained attention RT task. Pretask and post-task values were measured in the 2 min before, and in the 1 min after the task, respectively. It should be noted that post-task MEP values of the experimental group returned to the baseline level (i.e., the pretask values) and no significant difference was found between pre- and post-test MEP values ($P > 0.05$). This finding highlights a link between the act of sustaining attention and the rise in MEP amplitude. Vertical bars represent SD.

with the emergence of the TOT effect. A significant increase in CSE ($P < 0.01$) and in M1 area activity ($P < 0.05$) was also found, occurring, on average, after 15 min of the task ($P < 0.05$). Finally, we have shown that after 25 min of the task, medial frontopolar PFC activity significantly decreased compared with its peak activation during the 5th minute of the task ($P < 0.05$). Before focusing on a discussion of these neural activity changes throughout the TOT development, we first discuss a number of relevant methodological considerations.

Methodological Considerations

No significant difference was found between the groups with respect to the evolution of RT and the RPE estimation. Thus, the neurophysiological data (i.e., NIRS and TMS data) measured in both independent groups are discussed together.

It should be noted that muscle fatigue did not occur as a result of the sustained attention RT task, a fact supported by the absence of any significant difference between post- and pretask MVC values (Edwards 1981). Also, the absence of change in 1) the SP duration and the MEP/Hsup, MEPsup/Hsup, and MEP/M ratios, 2) Hsup/M ratio, and 3) M-wave amplitudes reveal that the repetition of thumb abduction during the experiment did not induce fatigue at 1) supraspinal, 2) spinal, and 3) muscle levels (Gandevia 2001). This eliminates these potential confounding factors from subsequent interpretations.

Finally, it was important to rule out the possibility that the changes in CSE were related to the repetitive contractions of the target muscle over the duration of the RT task and consequently the post task TMS measurements (see Fig. 5) were necessary to determine the nature of any such confounding influences. These TMS results demonstrate that in the 60 s following the task, CSE returned to a baseline level as measured during the pretask resting period. This suggests that the changes in CSE are more plausibly explained in terms of arising as a result of changes in sustained attention during the experiment. Also, it is noteworthy that there was no significant increase in CSE in the control group (Fig. 5), investigated with TMS but who were not required to perform RT. This result confirms that the increase in CSE measured over time in the group of the TMS experiment was isolated to the sustained attention RT task.

Increase in Lateral Prefrontal and Right Parietal Areas Activity After 10 min of Task

The results indicate that the TOT effect emerges after 9 min of the task ($P < 0.001$) and interestingly, that lateral PFC and right parietal areas activities begin to significantly increase ($P < 0.05$) at around the same time (10 min of task). Some electrophysiological (Fairclough et al. 2005) and neuroimaging studies (Paus et al. 1997; Weissman et al. 2006; Yarkoni et al. 2009) found similar results, with the time of occurrence of the reported increases in cortical activity and in RT depending on the cognitive load associated with the realized task. In particular, the NIRS results presented here strongly corroborate the findings resulting from the trial-by-trial analysis performed by Weissman et al. (2006) and reinforce the aforementioned interpretation of an increase in activation in response to increased attentional demand once the TOT effect occurs. According to Weissman et al. (2006), this increase in attentional demand follows—and is due to—the decrease in activity in

sensory structures which usually accompanies the occurrence of the TOT effect (e.g., Boksem et al. 2005). It is also worth considering the results reported here in terms of those from a recent study performed by De Joux et al. (2013) in which a decrease in left PFC oxygenation with the TOT effect occurrence was reported. The apparent conflict in terms of results should be considered in terms of differences of methods and instrumentation. For example, De Joux et al. (2013) do not report the location of their optical measurement channels, and may have investigated a different part of the left PFC area. Perhaps more significantly they exploited a discrimination task while we used a simple RT task (i.e., a detection task) and differences in attention-related cortical activation have been previously identified between these both types of task (Langner and Eickhoff 2013). Further investigation is required to better understand the role of the left PFC in discrimination versus detection tasks, especially in the context of attentional lapses.

In summary, our results demonstrate that activity in attention-related cortical areas increases in response to increased task demand across time; however, the data also reveal that neural adaptations to the TOT effect occurrence involve additional cerebral structures which have not traditionally been associated with attentional effects.

Increase in Corticospinal Excitability and M1 Activity After 15 min of Task

The experiments also reveal significant increases in CSE and M1 activity after 15 min of the task ($P < 0.01$ and $P < 0.05$, respectively). This suggests that the corticospinal tract and the M1 area are recruited in a complementary fashion with the attention-related areas in order to cope with the increasing task demand once the TOT effect occurs.

A number of previous studies have shown that shorter RTs, in contrast to longer RTs, were linked to 1) a larger increase in CSE during the movement preparation phase (Mars et al. 2007) and 2) greater activity in the M1 area (Oguz et al. 2003). However, the present study suggests that such patterns do not manifest themselves in the same way in the context of the TOT effect. In fact, the results here suggest that, despite the increase in CSE and M1 activity after 15 min, the RT continued to increase throughout the task (see Fig. 3). While such results could appear surprising at first we interpret instead that the increase in CSE and M1 activity does not occur to counteract the TOT effect development. Rather, we suggest that the observed activity patterns demonstrate how other brain areas are engaged to cope with the increased task demand that follows the disengagement of sensory structures accompanying the TOT effect occurrence (Boksem et al. 2005; Weissman et al. 2006).

It is important to note that the increase in cortical activity was not ubiquitous in terms of the set of motor structures investigated. In particular, PMC activity did not significantly change over time. The stability of PMC activity has at least 2 implications. First, it highlights that the NIRS-measured increase in M1 activity is certainly not due to a global systemic response in $[O_2Hb]$ over the motor cortical areas. Second, it suggests that the increase in CSE across time is not related to the activity of neural projections from the PMC which has direct access to the spinal cord (Dum and Strick 2002). Therefore, we can infer that the increased CSE across time was related to increased activity of projections from the M1 area.

This suggests that the increase in MEP amplitude may be the product of an increase in cortical neurons excitability and/or in spinal neurons excitability (for review, see Reis et al. 2008). As the timing of increase in amplitude for both the MEP and the NIRS-measured $\Delta[\text{O}_2\text{Hb}]$ over the M1 area (i.e., 15 min of task) are similar, one may suppose that the excitability was mainly increased at the cortical level. However, H-reflex results in humans (e.g., Schieppatti 1986) and intraspinal neural recordings in monkeys (e.g., Fetz et al. 2002) reported a facilitatory effect of motor preparation on spinal neurons activity. Further, it is notable that the NIRS-measured M1 activation resulted, in part, from the neuronal activation related to the execution of the motor response as well (i.e., it did not arise only as a result of the motor preparation neural activity). The hypothesis that there are motor preparation-related changes in spinal excitability after 15 min of task (maybe in parallel to the increase in M1 area activity) cannot be totally excluded. Further investigations of the modulation of spinal excitability with the TOT are required to test this hypothesis. Because of differences in excitability of the motoneuron pools as regards the upper and the lower limbs (Espirito et al. 2003) and in particular the significant difficulties in recording the H-reflex at rest over the upper limb, such measurements were not possible during our study. Our results present new questions regarding neural correlates of motor preparation in response to the occurrence of the TOT effect. For instance, investigating the possible changes in intracortical facilitation and inhibition and the modulation of spinal excitability related to motor preparation throughout a sustained attention task would allow investigators to distinguish how the different parts of the corticospinal tract adapt to lapses in attention.

Decrease in Medial PFC Activity After 25 min of Task

The final noteworthy observation from the data was that after 25 min of the task, medial frontopolar PFC activity significantly decreased ($P < 0.05$) compared with its peak activation at a point 5 min into the task. Again, this result corroborates an increase in the task demand as the TOT effect emerges. Indeed, as mentioned in the introduction, Fox et al. (2005) described that the more cognitively demanding the task, the higher the magnitude of the attention-related decreases and increases in brain activity. The frontopolar part of the medial PFC is known as one of the structures which reduces activity in response to attention-demanding tasks, as measured by means of fMRI (Gusnard and Raichle 2001) and NIRS (Pfurtscheller et al. 2010; Bauernfeind et al. 2011). As a consequence, the potential increase in the task demand over time might be responsible for driving the decrease in medial PFC activity.

One other (and complementary) potential interpretation involves a regional redistribution of cerebral blood volume (CBV) which would reflect both reduced medial PFC activity and concomitant increases in actively participating brain areas. Indeed, while global CBV is constant due to autoregulation mechanisms (Lassen 1964; Strandgaard and Paulson 1984), it is well known that CBV fluctuations happen regionally, as a function of local metabolic requirements. Lateral prefrontal, right parietal and M1 areas could belong to the regional areas requiring increased CBV with the TOT effect because of increased neural activity.

Conclusion

Overall, our study shows an increased involvement of key motor structures, including the corticospinal tract and the M1

cortical area, in response to the TOT effect occurrence during a sustained attention RT task. As it has been previously proposed for some attention-related areas, we suggest that these motor structures undergo increased activation because they have to cope with the increasing task demand. We report that the increased CSE and M1 activity occurs significantly later than the increase in lateral PFC and the right parietal areas activity (for this task) which suggests that the motor structures are only recruited at a later stage of the process. To the best of our knowledge, this study is the first to approach the question of the adaptations of the motor structures to lapses in attention. This work answers and opens new questions as regards the adaptation of motor structures' activity to the observed rise in RT over time, the so-called TOT effect.

Funding

This work was supported by the LabEx "Numerisation and Modelisation for Health and Environment" (ANR-10-LABX-20-01) and the French University Institute (IUF -UM1 1195-UM2 110744) through a PhD grant.

Notes

The authors thank the Languedoc-Roussillon Region council (AVENIR) for funding the NIRS equipment, Alain Varray for the use of the TMS equipment, and the engineer Jean-Paul MICALLEF for the development of experimental materials. *Conflict of Interest:* None declared.

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