The Norepinephrine System Affects Specific Neurophysiological Subprocesses in the Modulation of Inhibitory Control by Working Memory Demands

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Abstract: Inhibitory control processes are known to be modulated by working memory demands. However, the neurobiological mechanisms behind these modulations are inconclusive. One important system to consider in this regard is the locus coeruleus (LC) norepinephrine (NE) system. In the current study the role of the LC-NE system by means of pupil diameter recordings that are integrated with neurophysiological (EEG) and source localization data were examined. A combined mental-rotation Go/Nogo task was used. The results show that increases in working memory load complicate response inhibition processes. On a neurophysiological level these effects were reflected by specific modulations in event-related potentials (ERPs) reflecting motor inhibition processes (i.e., Nogo-P3). Attentional selection processes (reflected by the P1 and N1) as well as pre-motor inhibition or conflict monitoring processes (reflected by the Nogo-N2) were not affected. Activity of the LC-NE systems, as indexed by the pupil diameter data, predicted neurophysiological processes selectively in the Nogo-P3 time range. Source localization analyses suggest that this modulation occurs in the right middle and inferior frontal gyrus. The study provides evidence that the LC-NE system is an important neurobiological system modulating the effects of working memory load on response inhibition processes. More specifically, it modulates a subset of dissociable cognitive processes that are related to prefrontal cortical regions. *Hum Brain Mapp* 38:68–81, 2017. © 2016 Wiley Periodicals, Inc.

Key words: response inhibition; working memory; mental rotation; norepinephrine; EEG; pupil diameter; source localization

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INTRODUCTION

“Executive functions” is a generic term for a family of several cognitive processes that are important for goal-directed behavior [Diamond, 2013], usually comprising working memory, inhibition and cognitive flexibility. In this context decision making processes usually require an interplay of different executive functions in order to act adequately. For example, the ability to inhibit prepotent responses is limited by working memory capacity [Chmielewski et al., 2015b]. This limitation may occur because the information which response to inhibit must be retrieved from working memory. Alternatively this limitation might occur, as complex information may have to undergo a transformation in the working memory system in order to inform the actor whether to inhibit a response or not [Chmielewski et al., 2015b]. Moreover, response inhibition and working memory are assumed to be closely interrelated as both rely on a top-down strengthening of task-relevant representations; that is, the strengthening of the representation of the correct response, or respectively the strengthening of the task-relevant information [Braver and Barch, 2002]. This close interrelation of working memory and response inhibition processes also stands to reason from a functional neuroanatomical perspective, as the prefrontal cortical networks involved in response inhibition and working memory mechanisms largely overlap [Barch et al., 1997; Cohen et al., 1997; Curtis and D’Esposito, 2003; D’Esposito et al., 2000]. More specifically, the right inferior frontal cortex (rIFG) as well as the right medial frontal cortex are assumed to be involved in both response inhibition processes and working memory processes [Aron et al., 2004; Barch et al., 1997; Bari and Robbins, 2013; Criaud and Boulinguez, 2013]. In recent studies, increased task difficulty has consequently been shown to complicate response inhibition processes [Vaurio et al., 2009; Wodka et al., 2007]. On a neurophysiological (EEG) level it has been shown that increased working memory demands induced by mental rotation affect response inhibition processes by modulating the Nogo-P3 event-related potential (ERP) amplitude originating from the inferior and middle frontal gyrus [Chmielewski et al., 2015b]. This Nogo-P3 component has been suggested to reflect the act of inhibition itself [Beste et al., 2010c; Falkenstein et al., 1999; Huster et al., 2013; Schmajuk et al., 2006], a stimulus evaluation process [Friedman et al., 2001], or the inhibition outcome evaluation [Schmajuk et al., 2006]. As yet, the neurobiological mechanisms that modulate the effect of working memory demands on response inhibition mechanisms and their neurophysiological correlates still are inconclusive.

One neurobiological system that may be central for the interplay of working memory load and response inhibition is the norepinephrine (NE) system. NE is known to influence working memory through α -adrenoreceptors [Arnsen, 2000; Dash et al., 2007; Franowicz and Arnsten, 1998; Mao et al., 1999]. Interestingly, it has been suggested that

the P3 is an electrophysiological correlate of the locus coeruleus (LC) phasic NE response [Murphy et al., 2011; Nieuwenhuis et al., 2005]. In light of findings showing that especially response inhibition subprocesses reflected by the P3 are modulated by working memory load during response inhibition [Chmielewski et al., 2015b], this suggests that the LC-NE function may be central to understand the neurobiological mechanisms behind the interplay of working memory and response inhibition processes. A second reason why the LC-NE system may be of particular relevance is that this system is known to modulate task-related decision or selection processes [Aston-Jones and Cohen, 2005]. That is, phasic LC-NE responses are assumed to facilitate responses to task-relevant processes [Aston-Jones and Cohen, 2005; Nieuwenhuis et al., 2005] which should apply to response inhibition processes as modulated by varying demands on working memory in this study. Supporting this assumption, it has been shown that increasing norepinephrine (NE) concentrations in the prefrontal cortex improves response inhibition performance in rodents and humans [Chamberlain et al., 2007, 2009; Eagle et al., 2008].

We examine the relevance of the LC-NE system for the modulation of response inhibition processes by working memory load. To this end we integrate pupil diameter data with EEG data. Working memory load is operationalized by modulating the need for mental rotation processes by means of employing different rotation angles in a Go/Nogo paradigm [Chmielewski et al., 2015b]. Using EEG data we examine ERPs and perform source localization analyses. The pupil diameter was examined, as it has been suggested to be linked to phasic LC-NE activity, possibly due to shared major afferent pathways [Hou et al., 2005; Joshi et al., 2016; Murphy et al., 2011; Nieuwenhuis et al., 2011; Rajkowski et al., 1994]. Therefore, the pupil diameter is frequently used to examine LC-NE processes in relation to cognitive functions in humans [Gilzenrat et al., 2010; Hong et al., 2014; Jepma and Nieuwenhuis, 2010; Murphy et al., 2011]. In this context, higher NE concentrations are reflected by a larger pupil diameter [Hou et al., 2005; Phillips et al., 2000]. We hypothesize that changes in working memory load during response inhibition processes are reflected by changes in the pupil diameter. More specifically, we expect the pupil diameter and P3 amplitude to increase in the more complex Nogo conditions. Attentional selection processes may be of less importance, given results from previous studies show no modulation of these processes during response inhibition mechanisms modulated by working memory load [Chmielewski et al., 2015b]. Additionally, since it is assumed that the pupil diameter as well as neurophysiological processes are linked to activity of the LC-NE system, we expect that the pupil diameter and neurophysiological changes should be correlated. Regarding neurophysiological processes, especially Nogo-P3 amplitude modulations, related to activity in the medial frontal cortex and/or the lateral prefrontal

Block A		Block B	
left hand	right hand	left hand	right hand
<div> <div>6</div> <div>6</div> <div>6</div> <div>2</div> <div>2</div> <div>2</div> </div>	<div> <div>G</div> <div>G</div> <div>G</div> <div>7</div> <div>7</div> <div>7</div> </div>	Go	<div> <div>5</div> <div>5</div> <div>5</div> <div>2</div> <div>2</div> <div>2</div> </div>
<div> <div>6</div> <div>6</div> <div>6</div> <div>2</div> <div>2</div> <div>2</div> </div>	<div> <div>G</div> <div>G</div> <div>G</div> <div>7</div> <div>7</div> <div>7</div> </div>	NoGo	<div> <div>5</div> <div>5</div> <div>5</div> <div>2</div> <div>2</div> <div>2</div> </div>

Figure 1.

Overview of the experimental conditions in the mental rotation-Go/Nogo task. At the left side of the figure, block A is shown, the right side shows block B. For the Go (upper row) and Nogo (lower row) trials examples of the used stimuli are shown. For Go and NoGo trials it is indicated which stimulus required a left or a right hand response.

cortex, should be positively correlated with NE concentrations; that is, the pupil diameter.

MATERIALS AND METHODS

Participants

A total of $n = 25$ healthy young participants (18 female) between 18 and 30 years of age (mean age 23.3 ± 2.7) took part in the experiment. All participants were free of medication, had normal or corrected vision and reported no psychiatric or neurological disorders. Before the test protocol was conducted, written informed consent was obtained from all participants. The study was approved by the institutional review board of the Medical faculty of the TU Dresden and realized in accordance with the Declaration of Helsinki.

Task

To manipulate working memory load and its effect on response inhibition processes we used a paradigm, combining features of a classical Go/Nogo paradigm with a mental rotation paradigm. The paradigm used is identical to a previous study by our group [cf. Chmielewski et al., 2015b]: This task used rotated numbers and characters as stimuli. The task conditions are shown in Figure 1.

To ensure the classic characteristics of a Go/Nogo task, 30% Nogo trials requiring no response and 70% Go trials that required a specific response by the participants were utilized. The numbers 5 and 7 and the characters G and R were employed as target stimuli. These stimuli were chosen because they have a good visual discriminability and are known to not evoke sex-dependent differences in the mental rotation process [Heil et al., 2011; Jansen-Osmann

and Heil, 2007]. By means of target rotation, varying working memory load was induced in this Go/Nogo paradigm. Equal proportions of each target stimulus were rotated by 30°, 90°, or 150°, thus eliciting an increasing workload from the smallest to the largest rotation angle [Band and Kok, 2000; Koshino et al., 2005]. Targets were presented rotated clockwise and counter-clockwise in a normal (not mirrored) and a mirrored fashion [Beste et al., 2010a,b; Heil, 2002; Heil et al., 1998; Hoffmann et al., 2014].

Each trial began with an 800 ms presentation of a fixation cross, which was followed by 1,100 ms target presentation. Afterward a jittered 400–800 inter trial interval without any stimulus material was presented. Target presentation was terminated when a response was executed, irrespective if the response was correct or wrong. In the whole experiment 720 trials were presented in a randomized order. The trials were divided into two blocks with each block (360 trials) presenting 252 Go trials and 108 Nogo trials. The number of trials was equally distributed across the different rotation angles and mirror conditions. The two blocks of the experiment were included to further examine the impact of working memory load on response inhibition under alternating task complexity/-difficulty. As response inhibition processes were the main focus of this study the following denotation (less complex and complex block) of the two blocks refers a decreased or an increased difficulty to inhibit inappropriate responses (for Go trial block difficulty please refer to the end of this paragraph). As mentioned above, numbers and letters were chosen as targets, thus establishing two target categories (numbers vs. letters) that can easily be distinguished. In the less complex block A, all letters required a response, thus constituting the Go stimulus category. In contrast to that, all numbers required no response, thus constituting the Nogo stimulus category. Thus, Nogo trial processing was facilitated based on perceptual category information (letter vs. number). In other words, as soon as the target was identified as a number, mental rotation of the stimulus could be cancelled for these Nogo trials. On Go trials in block A, the presentation of a mirrored letter required a button press with the left hand, while the presentation of a normal (not mirrored) letter required a right hand response. In contrast to block A, numbers and letters were utilized as targets in the more complex block B. Here, task complexity/difficulty was increased in Nogo trials in comparison to block A, because participants could no longer benefit from the category information (letter vs. number). In this block, responses had to be carried out to un-mirrored targets, while mirrored numbers or letters required no response and thus served as Nogo trials. It was therefore necessary to perform mental rotation processes in order to decide whether or not to respond. These mental rotation processes increase the working memory load, thus allowing to examine the influence of mental workload on response inhibition processes. As both block A and B required a response to normal, un-mirrored

letters, transfer effects between the two blocks needed to be ruled out. To do so, normal, un-mirrored letters required a left hand response in block B (as compared with a right-hand response in block A). Consequently, the presentation of normal, un-mirrored numbers required a right hand response in block B. In order to provoke inhibition errors and to further amplify the effect of workload manipulation through time pressure, participants were generally requested to respond as fast and accurately as possible in each trial during the whole task [Chmielewski et al., 2015b]. Lastly, it should be noted that the logic of the denotation “less complex block A and complex block B” only refers to Nogo trials, which are focused in this study. Concerning Go trials the roles of the more and less complex block are reversed. That is, utilizing the correct response hand after having identified a trial as a Go trial (block A: letters; block B: non-mirrored letters and numbers) is divergently challenging in the two blocks. In line with the argumentation employed for NoGo trials, distinguishing between letters and number Go trials (block B) is easier than distinguishing between mirrored and non-mirrored letter Go trials (block A). Thus increased Go RTs and error rates would be expected in block A [Chmielewski et al., 2015b].

EEG and Pupil Diameter Recording and Analysis

EEG data was recorded from 60 Ag/AgCl electrodes arranged in equidistant positions. The sampling rate was 500 Hz and electrode impedances were kept below 5 k Ω . We used the same data analysis procedure as in a previous study [Chmielewski et al., 2015b]. A band-pass filter from 0.5 to 20 Hz (with a slope of 48 dB/oct each) and a notch filter at 50 Hz were applied and data was down-sampled to 256 Hz. Subsequently, an independent component analysis (ICA; infomax algorithm) was conducted on the un-epoched data sets in order to remove recurring artifacts. ICA components revealing blinks and pulse artifacts, horizontal and vertical eye movements were then manually discarded. Afterward, the EEG data was separately segmented for Go and Nogo trials: Go trials were only taken into account when the correct response was given in a time window of 1,200 ms after target onset. Likewise, Nogo trials were only included in subsequent data analysis when no response was given in the period up to 1,200 ms after stimulus presentation. Additionally, each condition (Go/Nogo) was further subdivided based on the employed block (less complex block A and complex block B) and based on the rotation angle (i.e., 30°/90°/150°). The segmentations were locked to the target stimulus, starting 1,000 ms before target presentation of the respective trial and ending 2,000 ms after its onset, thus resulting in 3 s segments. Subsequently, an automated artifact rejection procedure was conducted for all segments. An activity below 0.5 μ V in a 200 ms period and a maximal value difference of 200 μ V in a 100 ms interval were used as

rejection criteria. In order to eliminate reference potential from the data, a current source density (CSD) transformation [Nunez and Pilgreen, 1991] was then applied. The resulting CSD values are stated in μ V/m². Another reason for employing the CSD-transformation was that it serves as a spatial filter [Nunez and Pilgreen, 1991], which makes it possible to identify electrodes that best reflect activity related to cognitive processes. Afterward, a baseline correction from -200 to 0 ms prior to target onset was applied. For each category of segments, individual averages were calculated for every participant. The different ERP components, namely P1 (at P7 and P8: 90–110 ms after target presentation onset), N1 (at P7 and P8: 155–175 ms), Go/Nogo-N2 (at Cz: 246–380 ms), and Go/Nogo-P3 (at Cz: 450–700 ms) were identified by means of the scalp topography. To validate this choice of electrodes, the following procedure was applied [see also: Mückschel et al., 2014]: The mean amplitudes of the ERP components in the corresponding search intervals (see above) at all electrode positions were extracted. Subsequently, each electrode was compared against an average of all other electrodes using Bonferroni-correction for multiple comparisons (critical threshold $P = 0.0007$). Based thereon, only electrodes showing significantly larger mean amplitudes than the remaining electrodes in at least one of the different experimental conditions (negative or positive) were chosen. Essentially, the electrodes chosen that way were coherent with those found in the visual data inspection. After the choice of the corresponding electrodes, the peaks of all ERP components were semi-automatically picked and relocated if necessary.

During the experiment, the participants head was fixed in a skin rest. Pupil data was recorded using a RED 500 eye tracking device and the software iView X (SensoMotoric Instruments GmbH) using a 500 Hz sampling rate. The eye tracking device was calibrated prior to starting the task using a 9 point calibration. Eye blinks were automatically interpolated by the eye tracking recording software. For all subjects, the pupil diameter data in millimeter (mm) of both eyes was analyzed; that is, the mean pupil diameter of both eyes was used for data analysis. Pupil reactions from the left and right eye did not differ ($P > 0.93$) and were strongly correlated ($r > 0.94$). Pupil diameter data and EEG data were synchronized using the EYE-EEG extension [Dimigen et al., 2011] for EEGLab [Delorme and Makeig, 2004] (<http://www2.hu-berlin.de/eyetracking-eeG>). For analysis, the sampling rate was down-sampled to 256 Hz and a low pass filter was applied (IIR filter with 20 Hz at a slope of 48 dB/oct each). Remaining artifacts, for example artifacts related to eye blinks, were removed manually by means of a raw data inspection. Segmentation and baseline correction were conducted analog to the EEG data. To integrate the pupil diameter data and the EEG data, Pearson correlations were calculated between the pupil diameter data and the EEG data. Therefore, we first calculated the average of the

Figure 2.

(A) Reaction times (RTs) to the target stimuli (y-axis) are separately given for the different rotation angles (x-axis). Block A is given in black diamonds; block B is given in gray squares. (B) Frequency of Go trial errors (i.e., missed Go trials or choice errors on Go trials) (y-axis) for the different rotation angles (x-

axis). (C) Frequency of false alarms (y-axis) to NoGo stimuli for the different rotation angles (x-axis). In Figures B and C, black color denotes block A and gray color block B. The mean and standard error of the mean are always reported.

EEG and eyetracking data for each subject separately. These averaged data segments from $-2,000$ to $2,000$ ms locked on the stimulus (time point 0) were split into time bins of approximately 4 ms. This is the length of each sampling point after downsampling the data to a resolution of 256 Hz (refer processing steps of the data above). Then, every EEG data time bin was correlated with every pupil diameter data time bin across all participants.

Source Localization Analysis

To examine which functional neuroanatomical networks related to modulations in cognitive neurophysiological subprocesses source localization analyses were conducted using sLORETA [standardized low resolution brain electromagnetic tomography; Pascual-Marqui, 2002]. It gives a single linear solution to the inverse problem, based on extra-cranial measurements without a localization bias [Marco-Pallarés et al., 2005; Pascual-Marqui, 2002; Sekihara et al., 2005]. There is also evidence of from EEG/fMRI and neuronavigated EEG/TMS studies underlining the validity of the sources estimated using sLORETA [Dippel and Beste, 2015; Sekihara et al., 2005]. For sLORETA, the intra-cerebral volume is partitioned into 6,239 voxels at 5 mm spatial resolution. The standardized current density at each voxel is calculated in a realistic head model [Fuchs et al., 2002] using the MNI152 template [Mazziotta et al., 2001]. In this study, the voxel-based sLORETA images were calculated using the sLORETA-built-in voxel-wise randomization tests with 2,000 permutations, based on statistical nonparametric mapping (SnPM). Significant voxels with significant differences ($P < 0.01$, corrected for multiple comparisons) were located in the MNI-brain.

Statistics

Behavioral data, that is, Go reaction times, frequency of Go errors (i.e., missed Go trials or choice errors on Go

trials) and frequency of Nogo false alarms (i.e., button presses on Nogo trials) were analyzed with repeated-measures ANOVAs. Behavioral data was analyzed using the within-subject factors “block” (less complex block A, complex Block B) and “rotation angle” (30° , 90° , 150°). For the neurophysiological data “condition” (Go/Nogo) and “electrode” (electrode sites at which the P1 and N1 ERP effects were quantified) were included in the model as additional within-subject factors. For the eyetracking data, a repeated measures ANOVA employing the factors “condition,” “block,” and “rotation angle” was conducted with averaged pupil diameters. Greenhouse–Geisser correction was applied wherever appropriate and all post-hoc tests were Bonferroni-corrected. As indicated by Kolmogorov–Smirnov tests, all variables analyzed were normal distributed (all $z < 0.9$; $P > 0.3$). Lastly, correlations between the Nogo EEG data and the Nogo pupil diameter were analyzed by means of mean determination coefficient R^2 for each rotation angle in each block.

RESULTS

Behavioral Data

Go reaction times (RTs), Go error frequency, and Nogo false alarm frequency are shown in Figure 1 for block A and block B. The mean and standard error of the mean (SEM) are reported for the descriptive data.

The ANOVA for Go reaction time data (Fig. 2A) revealed a main effect of block ($F(1,20) = 4.66$; $P = 0.043$; $\eta^2 = 0.189$) showing that Go RTs were slower in the less complex block A ($664 \text{ ms} \pm 14$) than in the complex block B ($640 \text{ ms} \pm 14$). Furthermore, a main effect of rotation angle ($F(2,40) = 127.47$; $P < 0.001$; $\eta^2 = 0.864$) was observed. Post-hoc paired t-tests revealed that RTs increased with the rotation angle (30° : $613 \text{ ms} \pm 12$; 90° : $636 \text{ ms} \pm 13$; 150° : $707 \text{ ms} \pm 16$) (all $t > 6.20$; $P \leq 0.001$). No interaction of block

× rotation angle could be detected ($F(2,40) = 1.78$; $P = 0.082$), as can be seen in Figure 2A.

For Go errors (i.e., missed Go trials or choice errors on Go trials) (Fig. 2B), the ANOVA revealed a main effect of block ($F(1,20) = 4.90$; $P = 0.039$; $\eta^2 = 0.197$), showing that the frequency of Go errors was higher in the less complex block A (14.2 ± 1.7) than in complex block B (10.3 ± 1.4). Additionally, a main effect of rotation angle ($F(2,40) = 17.43$; $P < 0.001$; $\eta^2 = 0.466$) was observed. That is, the frequency of errors increased with increasing angular displacement (30° : 8.6 ± 1.4 ; 90° : 9.3 ± 1.1 ; 150° : 18.8 ± 2.4). Post-hoc paired t -tests, however, revealed that only the 150° condition differed from the two other conditions (all $t \geq 4.85$, $P \leq 0.001$), while the 30° and 90° condition did not differ from each other ($t(22) = 0.99$; $P = 0.334$). Furthermore, an interaction of block × rotation angle ($F(2,40) = 20.09$; $P < 0.001$; $\eta^2 = 0.501$) was detected as shown in Figure 2B. As the two blocks differ in the necessity to employ mental rotation processes in order to categorize stimuli as Gos or Nogos, the two blocks were separately analyzed with repeated measures ANOVAs to further examine the interaction. In the less complex block A, a main effect of rotation angle was observed ($F(2,44) = 23.60$; $P < 0.001$; $\eta^2 = 0.518$), showing that the number of Go errors increased with increasing angular displacement. The same main effect of rotation angle could be found in the complex block B ($F(2,44) = 6.53$; $P = 0.003$; $\eta^2 = 0.229$), although the effect size (η^2) was much smaller. This shows that effects of angular displacement had a stronger influence on the frequency of Go errors in the less complex block A than in the complex block B.

The frequency of false alarms (see Fig. 2C) is, however, the most important behavioral parameter in Go/Nogo tasks. For the frequency of false alarms, the ANOVA revealed a main effect of block ($F(1,20) = 27.59$; $P < 0.001$; $\eta^2 = 0.580$), that is, more false alarms were committed in the complex block B (2.9 ± 0.5) than in the less complex block A (0.6 ± 0.2). Most importantly, an interaction block × rotation angle was detected ($F(2,40) = 3.97$; $P = 0.027$; $\eta^2 = 0.165$). As already mentioned above, as the two blocks differ in the necessity to employ mental rotation processes in order to categorize stimuli as Gos or Nogos, the two blocks were separately analyzed with repeated measures ANOVAs to further examine this interaction. In the less complex block A, no main effect of rotation angle could be detected ($F = 0.53$; $P = 0.591$). In contrast to that, a main effect of rotation angle was detectable in the complex block B ($F(2,44) = 3.77$; $P = 0.031$; $\eta^2 = 0.146$) (30° : $0.3.0 \pm 0.65$; 90° : 2.8 ± 0.532 ; 150° : 4.61 ± 0.86). Post-hoc paired t -tests revealed significant differences between the 150° condition and the other two conditions (all $t \geq 2.64$, $P \leq 0.015$), but no significant difference between the 30° and 90° conditions ($t(22) = 0.32$, $P = 0.749$). Thus, the detected interaction was mostly driven by a significant increase in false alarms in the 150° condition as compared with the other two rotation angles in the more challenging block B.

Neurophysiological Data

No effects of ERP peak latency were detected in all of the assessed neurophysiological data (all $F < 0.9$; $P > 0.5$).

P1 Effects

In Figure 3, P1 and N1 ERPs are shown for Go and Nogo trials in block A and block B.

For P1 amplitudes, the repeated measures ANOVA using block, electrode, condition, and rotation angle as within-subject factors yielded the following results: A main effect of rotation angle was obtained ($F(2,40) = 4.64$; $P = 0.015$; $\eta^2 = 0.189$), showing an decreased P1 amplitude in the 90° ($35.2 \mu\text{V}/\text{m}^2 \pm 4.4$) rotation angle (all $t \geq 2.21$, $P \leq 0.015$) in comparison to the other two rotation angles (30° : $37.5 \mu\text{V}/\text{m}^2 \pm 4.5$; 150° : $37.1 \mu\text{V}/\text{m}^2 \pm 4.5$). Moreover an interaction condition × block was obtained ($F(1,20) = 13.92$; $P = 0.001$; $\eta^2 = 0.410$) and an interaction electrode × condition × block was obtained ($F(1,20) = 6.40$; $P = 0.020$; $\eta^2 = 0.242$). When further analyzing this interaction in both blocks separately, in electrode P7 an interaction condition × block could be observed ($F(1,20) = 6.92$; $P = 0.016$; $\eta^2 = 0.257$), while in electrode P8 the exact same interaction could be observed ($F(1,20) = 13.79$; $P = 0.001$; $\eta^2 = 0.408$), even though the effect size (η^2) was bigger. This suggests that this interaction effect is only due to activation differences between the two electrodes.

N1 Effects

A repeated measures ANOVA using electrode, condition, block, and rotation angle as within-subject factors was conducted for the N1 amplitudes. In this ANOVA a main effect of rotation angle was obtained ($F(2,40) = 4.60$; $P = 0.016$; $\eta^2 = 0.187$), showing N1 activity to increase from the 150° ($57.8 \mu\text{V}/\text{m}^2 \pm 7.5$) to the 30° ($59.3 \mu\text{V}/\text{m}^2 \pm 7.7$) to the 90° ($61.4 \mu\text{V}/\text{m}^2 \pm 7.8$) rotation angle. Post-hoc paired t -tests only revealed significant differences between the 90° and the other two rotation angles (all $t \geq 2.21$, $P \leq 0.039$), while the 30° and the 150° rotation angle did not differ ($t(20) = 0.58$, $P = 0.566$). Moreover a significant interaction electrode × condition was observed ($F(2,40) = 14.42$; $P = 0.001$; $\eta^2 = 0.419$). Post-hoc paired t -tests showed that this difference was due to significant differences in N1 amplitude between P7 and P8 Nogo trials ($t(20) = 8.68$, $P < 0.001$), while N1 amplitude between Go at P7 and at P8 did not differ ($t(20) = 0.29$, $P = 0.777$).

N2 Effects

The N2 and P3 potentials on Go and Nogo trials for block A and block B are shown in Figure 4. Please note that peak-to-peak amplitudes were employed in the ANOVAs. Please note that in the red box on the right side averaged scalp topographies of all Nogo-P3 conditions,

Figure 3.

PI and NI components evoked by the target stimuli (averaged between electrodes P7 and P8 for the different rotation angles). The y-axis denotes $\mu\text{V}/\text{m}^2$ and the x-axis denotes the time in s. The left side shows Go trials, the right side NoGo trials. The green lines denote the ERPs in the 30°, red lines in the 90°, and blue lines in the 150° rotation angle condition. For the less complex block A lighter colors are used, while for the more

complex block B darker colors are employed. The scalp topography plots denote the distribution of the ERPs averaged between all different rotation angles for both blocks, showing that the PI and NI clearly centered around electrodes P7 and P8. Warm colors indicate positive and cold colors denote negative deflections. [Color figure can be viewed at wileyonlinelibrary.com.]

which were created by means of employing a baseline at the time window of the N2, are depicted in order to underline the choice of the Cz for the P3 analysis.

A repeated measures ANOVA using block, condition, and rotation angle was conducted for the N2 amplitudes. In this ANOVA a main effect of rotation angle was obtained ($F(2,40) = 4.41$; $P = 0.019$; $\eta^2 = 0.187$), showing N2 activity to increase from the 30° ($38.1 \mu\text{V}/\text{m}^2 \pm 2.4$) to the 90° ($39.8 \mu\text{V}/\text{m}^2 \pm 2.6$) to the 150° ($41.3 \mu\text{V}/\text{m}^2 \pm 2.8$) rotation angle. Post-hoc paired t -tests only revealed a significant difference in N2 amplitudes between 30° and 150° rotation angle ($t(20) = 3.22$, $P = 0.004$), while the 90° condition neither differed from the 30°, nor from the 150° rotation angle (all $t \leq 1.62$, $P \leq 0.120$). Moreover an interaction condition $\times$ rotation angle reached significance ($F(2,40) = 3.41$; $P = 0.043$; $\eta^2 = 0.146$). Post-hoc t -tests revealed this interaction to be based on a significant difference between 90° Go and Nogo trial N2 amplitude ($t(20) = 2.10$, $P = 0.048$), while the in the 30° and the 150° rotation angle Go and Nogo trial N2 amplitude did not differ (all $t \leq 2.04$, $P \geq 0.055$). Besides that, the interaction block $\times$ rotation angle was observed ($F(2,40) = 826$; $P = 0.001$; $\eta^2 = 0.292$). Post-hoc t -tests showed this interaction to be based on significant differences between all rotation angles in the complex block B (all $t \geq 2.27$, $P \leq 0.034$), while no significant differences were obtained in the less complex block A (all $t \leq 1.44$, $P \geq 0.166$). This supports the assumption that rotation processes are not necessary in the less complex block A.

P3 Effects

A further repeated measures ANOVA using block, condition, and rotation angle was conducted for the P3 amplitudes. In this ANOVA a main effect of rotation angle was obtained ($F(2,40) = 8.95$; $P = 0.001$; $\eta^2 = 0.309$), showing P3 activity to increase from the 30° ($32.7 \mu\text{V}/\text{m}^2 \pm 1.9$) to the 90° ($36.5 \mu\text{V}/\text{m}^2 \pm 2.0$) to the 150° ($36.7 \mu\text{V}/\text{m}^2 \pm 2.4$) rotation angle. Post-hoc paired t -tests only revealed a significant difference in P3 amplitudes between the 30° rotation angle and the other two conditions (all $t \geq 3.27$, $P \leq 0.004$), while the 90° and 150° rotation angle did not differ ($t(20) = 0.27$, $P = 0.790$). Moreover an interaction condition $\times$ rotation angle ($F(2,40) = 5.51$; $P = 0.008$; $\eta^2 = 0.216$) and an interaction condition $\times$ block $\times$ rotation angle were detected ($F(2,40) = 4.08$; $P = 0.024$; $\eta^2 = 0.170$). The latter interaction was then analyzed for each block separately. In the less complex block A only a main effect of condition was observed, showing that the Go trial P3 amplitude ($34.1 \mu\text{V}/\text{m}^2 \pm 3.7$) was significantly smaller than the Nogo trial P3 amplitude ($43.8 \mu\text{V}/\text{m}^2 \pm 4.9$). In contrast to that in the complex block B a main effect of condition ($F(1,22) = 14.45$; $P = 0.001$; $\eta^2 = 0.396$), a main effect of rotation angle ($F(2,40) = 9.92$; $P < 0.001$; $\eta^2 = 0.311$) and an interaction condition $\times$ rotation angle ($F(2,40) = 8.14$; $P = 0.001$; $\eta^2 = 0.270$) were observed. Post-hoc paired t -tests revealed that this interaction was only due to significant differences between the 30° Nogo trials ($30.5 \mu\text{V}/\text{m}^2 \pm 2.0$)

Figure 4.

N2 and P3 components evoked by the target stimuli at electrode Cz. The y-axis denotes $\mu\text{V}/\text{m}^2$ and the x-axis denotes the time in s. The left side shows Go trials, the right side NoGo trials. The green lines denote the ERPs in the 30°, red lines in the 90°, and blue lines in the 150° rotation angle condition. For the less complex block A lighter colors are used, while for the more complex block B darker colors are employed. The scalp topography plots on the left side (Go trials) denote the distribution of the ERPs averaged between all different rotation angles for both blocks, showing that the N2 is clearly centered at electrode Cz. The scalp topography plots on the right side (NoGo trials) denote the

distribution of the ERPs for all different rotation angles for both blocks, showing that the N2 is clearly centered at electrode Cz. In the red box averaged scalp topographies of all P3 conditions, which were created by means of employing a baseline at the time window of the N2, are depicted in order to underline the choice of the Cz for the P3 analysis. Warm colors indicate positive, and cold colors denote negative deflections. Please note that for the statistics peak-to-peak amplitudes were employed. Thus the observable values in the graphic deviate from the values stated in the text. [Color figure can be viewed at wileyonlinelibrary.com.]

and the other two Nogo conditions (90°: $40.9 \mu\text{V}/\text{m}^2 \pm 3.4$, 150°: $41.8 \mu\text{V}/\text{m}^2 \pm 3.1$; all $t \geq 3.33$, $P \leq 0.003$), while the 90° and 150° NoGo trials ($t(22) = 0.48$, $P = 0.636$) did not differ. In contrast to that, there were no significant differences between the different rotation angles in the Go trials (all $t \leq 0.93$, $P \geq 0.363$).

Thus far, the electrophysiological data suggest that specific response inhibition subprocesses are modulated by working memory load (i.e., the Nogo-P3). Other electrophysiological correlates of response inhibition subprocesses (i.e., Nogo-N2) and attentional selection processes (P1, N1) did not reflect the modulatory pattern observed in the behavioral data.

Pupil Diameter Data and Integration with EEG Data

The pupil diameter data is shown in Figure 5.

As can be seen in Figure 5A, the pupil diameter was modulated differently at various time points by the

mental rotation Go/Nogo task. The repeated-measures ANOVA revealed no significant effects for the peak of the first pupil dilation around 200–300 ms after stimulus onset, neither for the peak pupil diameter (all F 's < 1.54 ; $P > 0.22$), nor for the peak latency (all F 's < 2.65 ; $P > 0.08$). For the peak of the first pupil constriction (500–800 ms after stimulus onset), a significant main effect of rotation angle indicates that the size of the constriction differed significantly between the different rotation angles ($F(2,40) = 4.23$; $P = 0.022$; $\eta^2 = 0.18$). Post-hoc pair-wise comparisons showed that the pupil diameter was smaller at 30° rotation angle ($-0.091 \text{ mm} \pm 0.017$) compared with trials with a rotation angle of 90° ($-0.079 \text{ mm} \pm 0.018$; $P = 0.029$), or 150° ($-0.077 \text{ mm} \pm 0.018$; $P = 0.026$). The 90° and 150° rotation angle trials did not differ. All other effects were not significant (all F 's < 1.87 ; $P > 0.187$). For the peak latency of the first pupil constriction the ANOVA revealed a significant main effect of condition ($F(1,20) = 21.94$; $P < 0.001$; $\eta^2 = 0.52$). The peak latency was shorter in Go trials ($621.16 \text{ ms} \pm 18.39$) than in Nogo

Figure 5.
(See legend on the following page.)

trials (716.83 ± 23.40). All other effects were not significant (all F 's < 3.57 ; $P > 0.07$).

Concerning the second pupil dilation, around 1,200 ms for NOGO trials and 1,400–1,600 ms for GO trials, a significant main effect of condition was obtained ($F(1,20) = 83.67$; $P < 0.001$; $\eta^2 = 0.81$) showing that the pupil diameter was larger in Go trials ($0.117 \text{ mm} \pm 0.013$) than in Nogo trials ($-0.009 \text{ mm} \pm 0.018$). The main effect of rotation angle indicated that the second dilation also differed significantly between rotation angles ($F(1.46,29.18) = 8.64$; $P = 0.003$; $\eta^2 = 0.30$). The pupil diameter was smaller in 30° trials ($0.039 \text{ mm} \pm 0.015$) in comparison to 90° ($0.057 \text{ mm} \pm 0.014$; $P = 0.005$) and 150° trials ($0.067 \text{ mm} \pm 0.015$; $P = 0.001$). No difference was found between 90° and 150° trials. All other effects were not significant (all F 's < 2.43 ; $P > 0.11$). Regarding the peak latency of the second pupil dilation, the ANOVA revealed a significant main effect of condition ($F(1,20) = 108.81$; $P < 0.001$; $\eta^2 = 0.85$). The second dilation peaked later in Go trials ($1461.28 \text{ ms} \pm 32.05$) compared with Nogo trials ($1171.26 \text{ ms} \pm 32.95$). All other effects were not significant (all F 's < 2.26 ; $P > 0.15$). The second pupil constriction was only determined for Nogo trials in a time window of 1,400–1,600 ms. The ANOVA revealed a main effect of block ($F(1,20) = 10.07$; $P = 0.005$; $\eta^2 = 0.335$). The pupil diameter of the second constriction was smaller (i.e., less negative) in trials of the complex block B ($-0.061 \text{ mm} \pm 0.021$) compared with trials in the less complex block A ($-0.109 \text{ mm} \pm 0.024$). All other effects were not significant (all F 's < 0.14 ; $P > 0.87$). For the peak latency of the second constriction, no effects were found (all F 's < 2.16 ; $P > 0.15$).

To directly integrate the pupil diameter data with the EEG data, Pearson correlations were calculated between the pupil diameter data and the EEG data. For this, we correlated pupil diameter and ERP amplitude values at each time point of an epoch across all participants. Yet, since the ERP analyses show that effects of working memory load (i.e., rotation angle) on response inhibition processes were reflected by the Nogo-P3 at electrode Cz, these correlation analyses were restricted to that electrode.

Figure 5B shows the results of this analysis for the different rotation conditions in the less complex block A and the complex block B. Only significant correlations are shown. Positive correlations are marked in orange, negative correlations are marked in blue. For the complex block B it is shown that significant positive correlations between the pupil diameter data between 0 and 600 ms and the ERP amplitude values were obtained between 350 and 800 ms. The mean correlation coefficient (r_{mean}) in the obtained cluster was $r_{\text{mean}} = 0.529$; $R^2 = 0.28$; $P < 0.015$ for the 30° condition, $r_{\text{mean}} = 0.538$; $R^2 = 0.29$; $P < 0.015$ for the 90° degree condition and $r_{\text{mean}} = 0.543$; $R^2 = 0.29$; $P < 0.013$ for the 150° condition. The correlations were, thus, obtained for the time interval of the Nogo-P3. Before and after this time intervals no significant correlations were obtained. The same results are obtained when running the correlation analyses in the less complex block A. There, the mean correlation coefficient (r_{mean}) in the obtained cluster was $r_{\text{mean}} = 0.548$; $R^2 = 0.30$; $P < 0.014$ for the 30° condition, $r_{\text{mean}} = 0.458$; $R^2 = 0.21$; $P < 0.031$ for the 90° condition and $r_{\text{mean}} = 0.531$; $R^2 = 0.28$; $P < 0.017$ for the 150° condition. However, as can be seen in Figure 5B, the size of the cluster of significant correlation obtained was smaller in the less complex block A (30° : 1,080; 90° : 363; 150° : 222) compared with the complex block B (30° : 1,978; 90° : 1,519; 150° : 1,860) in each rotation angle condition. While these analyses show that processes reflected by the Nogo-P3 probably are linked to the norepinephrine system, they do not inform about the functional neuroanatomical structures which are related to these modulations. We, therefore, performed a sLORETA analysis in which we calculated the source of the mean EEG activity in the time interval showing significant correlations between the pupil diameter data and the ERP data (i.e., the time interval between ~350 and 800 ms). The results, which were corrected for multiple comparisons ($P < 0.01$) using randomization test with 2,000 permutations based on statistical nonparametric mapping (SnPM), showed that in all rotation angle conditions in the complex block B brain regions including the right middle frontal gyrus (rMFG) and the

Figure 5.

Integration of pupil diameter data. (A) Pupil diameter data for Go and Nogo conditions for the less complex block A and the complex block B in the three different rotation angles 30° , 90° , and 150° . The y-axis denotes mm and the x-axis denotes the time in s. (B) Correlation plots of pupil diameter data and electrophysiological data at electrode Cz. Correlation plots are given for the Nogo condition, separately for each rotation angle as well as for less complex block A and complex block B. The colors denote significant r-values, with positive correlations denoted in orange colors and negative correlations denoted in blue colors. Correlation data is plotted in the time range from -1 s before stimulus presentation until 2 s after stimulus presentation. The x-axis and the y-axis denote time in s. The

horizontal and vertical dotted white lines denote the time point of stimulus presentation. The dashed white square indicates the time window used for determination of the mean determination coefficient R^2 . (C) Results of source localization analysis using sLORETA. The activation differences were obtained by contrasting less complex block A and complex block B in the time interval showing significant correlations between the pupil diameter data and the ERP data (0.35–0.8 s). Only significant activation differences ($P < 0.01$) as obtained on the basis of randomization tests are depicted. For all contrasts significant activation differences were found in the right middle frontal gyrus (rMFG) and right inferior frontal gyrus (rIFG). [Color figure can be viewed at wileyonlinelibrary.com.]

right inferior frontal gyrus (rIFG) were modulated (refer Fig. 5C).

However, above correlation analyses were calculated across subjects. An analysis showing within-subject correlations using single trial ERPs and single trial pupil diameter data is shown in the Supporting Information. There, however, no reliable correlations of pupil diameter data and ERP data were obtained ($r = -0.051$; $P = 0.525$).

DISCUSSION

In the current study we examined the relevance of the norepinephrine system for the modulation of inhibitory control processes by means of diverse working memory demands. This was realized using a system neurophysiological approach integrating pupil diameter data with EEG and source localization data. The pupil diameter is a frequently used parameter to examine LC-NE processes in relation to cognitive functions [Gilzenrat et al., 2010; Hong et al., 2014; Jepma and Nieuwenhuis, 2010; Joshi et al., 2016; Murphy et al., 2011] with higher NE concentrations being reflected by a larger pupil diameter [Hou et al., 2005; Phillips et al., 2000]. In a given task, the continuous recording of the pupil diameter in combination with ERPs offers the opportunity to examine for which cognitive subprocess and at which precise time point during information processing the NE system is of importance.

The behavioral data replicated the findings of the previous study [Chmielewski et al., 2015b]. Most important, the false alarm data show that working memory load modulated response inhibition performance. This was, however, only the case in the task block in which the decision to respond or to withhold the response could not be reached on the basis of perceptual categorization processes (less complex block A), but required a mental rotation of stimuli (complex block B). There (in block B), increasing rotation angles were related to a higher rate of false alarms, showing that increasing working memory load [Shepard and Metzler, 1971, 1988] complicates response inhibition processes. There was, however, no successive increase of false alarms with increasing rotation angles, as the 30° and 90° rotation conditions did not differ from each other. This finding also replicates recent results using this task [Chmielewski et al., 2015b] and can be explained by the fact that people are more familiar with stimuli rotated by 90°, which might facilitate the processing of such stimuli [Neely and Heath, 2011]. The neurophysiological (ERP) data reflected block and rotation angle dependent modulations of response inhibition processes only for the Nogo-P3, but not for the Nogo-N2 data, which is also in line with recent findings [Chmielewski et al., 2015b]. This suggests that pre-motor inhibition processes of intended movements, reflected by the Nogo-N2 [Beste, et al., 2010c; Falkenstein et al., 1999; Jodo and Kayama, 1992; Lavric et al., 2004] are not reflected. In contrast, processes related to the act of inhibition itself [Beste et al., 2010c;

Chmielewski et al., 2015a; Dippel et al., 2015; Falkenstein et al., 1999; Huster et al., 2013; Polich, 2007; Schmajuk et al., 2006], or even the evaluation of the outcome of the inhibition process [Schmajuk et al., 2006; Wu and Zhou, 2009] were modulated.

Modulations were also evident in the pupil diameter data. Concerning the first pupil constriction and the second pupil dilation it could be shown that the pupil diameter was smallest in the 30° condition and increased with increasing rotation angles. This is in line with the assumptions that pupil dilation might be an indicator of working memory load/mental effort [Kahneman and Beatty, 1966]. This interpretation is supported by the block effect observed in the second constriction. In the more complex block in which working memory load was increased, the pupil dilation was larger in comparison to the less complex block, which involved no mental rotation processes. The increased pupil size in Go trials in comparison to Nogo trials may be explained by the fact that Go trials were terminated directly after the response, while correctly inhibited Nogo trials were presented for the whole 1,200 ms.

The integration of the ERP data with the pupil diameter data revealed a cluster of significant positive correlations in a time window between approximately 350 and 800 ms and thus selectively in the time window of the Nogo-P3. Hence, the pupil diameter was only predictive for the neurophysiological (ERP) data in the time window of the Nogo-P3. Larger pupil diameters were related to a larger Nogo-P3. Interestingly, these correlations with the ERP variations were obtained for the pupil diameter data in a time range around the presentation of the Nogo-stimuli and therefore well before the onset of the Nogo-P3. Considering that the pupil diameter as correlate of phasic LC activity has a response latency of about 200–500 ms [Joshi et al., 2016; Nieuwenhuis et al., 2011], the correlation results suggest that the pupil diameter may have been modulated by NE activity in the time range around stimulus presentation. The early activity of the LC-NE system around stimulus onset may be important to prepare the cognitive control/response inhibition system, as indicated by the P3, to work efficient. Since higher NE concentrations are known to be reflected by a larger pupil diameter [Hou et al., 2005; Phillips et al., 2000] it seems that higher NE concentrations, or higher LC-NE system activity improves subsequent inhibitory control processes. This is in line with pharmacological studies on NE effects in inhibitory control [Chamberlain et al., 2007, 2009; Eagle et al., 2008]. The correlation was evident for all rotation angle conditions in block B, that is, the block in which mental rotation processes were necessary to decide whether to respond or to withhold a response. When no mental rotation was required (i.e., in block A) and where response inhibition was thus easier to process (cf. false alarm rate data), the cluster of correlations was smaller (i.e., the number of significantly correlated time points was lower). Overall, this pattern of results underlines assumptions that

the P3 can be regarded as an electrophysiological correlate of the locus coeruleus (LC) phasic NE response [Murphy et al., 2011; Nieuwenhuis et al., 2005]. Processes probably reflecting the act of inhibition itself or even the evaluation of the outcome of the inhibition process [Beste et al., 2010c; Falkenstein et al., 1999; Huster et al., 2013; Polich, 2007; Schmajuk et al., 2006; Wu and Zhou, 2009] might have been modulated by the LC-NE system. This effect occurred in a time range around the presentation of the stimulus. Hence, the LC-NE system may constitute an initial activating, driving force, adjusting the level of “preparedness” for further processing of relevant stimuli, thereby augmenting performance for the current task [Aston-Jones and Cohen, 2005; Berridge and Waterhouse, 2003]. In the current study, these processes were related to the decision to respond or to refrain from responding. Interestingly, the size of the cluster with significant correlations was larger in the complex block B, than in the less complex block A. This may suggest that the modulation of response inhibition processes by the LC-NE system is particularly important when working memory processes are central to inform the decision to execute a response or to refrain from responding. In fact, it has been shown that the administration of drugs increasing NE receptor activity in the PFC improves performance on a variety of PFC-dependent working memory related tasks [Franowicz and Arnsten, 1998; Salgado et al., 2016]. The obtained positive correlations between pupil diameter and Nogo-P3 (i.e., higher NE concentrations are related to a higher Nogo-P3) are in line with this. To examine the functional neuroanatomical network related to these modulatory effects we calculated the neuronal source of ERP modulations for the time window showing the positive correlations between pupil diameter and ERP amplitudes using sLORETA. These analyses showed brain areas including the right middle frontal gyrus (rMFG) and right inferior frontal gyrus (rIFG) to be active during the time interval. These regions have frequently been reported to be involved in response inhibition processes [Aron et al., 2004; Bari and Robbins, 2013; McNab et al., 2008; Rubia et al., 2001] and working memory processes [Barch et al., 1997; D’Esposito et al., 2000]. It therefore seems that phasic LC-NE activity, as indexed by the pupil diameter, modulates working memory dependent variations in response inhibition processes by affecting neuronal processes in the right inferior frontal cortex and hence cortical regions that constitute parts of a response inhibition network. This is possible because especially the dorsolateral and orbitofrontal cortex show strong direct anatomical connections to the LC [Arnsten and Goldman-Rakic, 1984] and are therefore likely to be modulated by the effects of norepinephrine. As to be expected no correlation of the pupil data was obtained in the time range of the N2. This stands to reason, as pupil size is assumed to be related to the LC-NE activity [Nieuwenhuis et al., 2005], while the N2 and thus premotor inhibition processes are assumed to be triggered by a

dopaminergic innervation emerging from nigrostriatal regions of the brain [Beste et al., 2010c].

However, concerning the correlation analyses using pupil diameter data and ERPs it needs to be noted that correlations were only obtained across participants, but no correlations were obtained when calculating within-subject correlations between single trial ERPs and single trial pupil diameter data. It cannot be ruled out that the effects obtained for the between-subject correlations are affected by several other factors unrelated to the LC-NE system (e.g., skull thickness, personality traits etc.). The results of the within-subject analysis may be interpreted as evidence for this. However, such within-subjects correlations are also not without problems. This is because these correlations need to be calculated on the single trials ERP and pupil diameter data. Data used for these calculations have a lower signal-to-noise ratio (i.e., are noisier), which affects correlation analyses.

In summary, the study provides evidence that the LC-NE system is an important neurobiological system modulating the effects of working memory load on response inhibition processes. Increases in working memory load complicate response inhibition processes. On a neurophysiological level these effects were reflected by specific modulations in ERPs reflecting motor inhibition processes (i.e., Nogo-P3). Attentional selection processes as well as premotor inhibition or conflict monitoring processes were not affected. Activity of the LC-NE predicted neurophysiological processes selectively in the Nogo-P3 time range. Source localization analyses suggest that this modulation occurs in the right middle and inferior frontal gyrus. The study provides evidence that the LC-NE system is an important neurobiological system modulating the effects of working memory load on response inhibition processes.

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