Noradrenergic Regulation of Cognitive Flexibility: No Effects of Stress, Transcutaneous Vagus Nerve Stimulation, and Atomoxetine on Task-switching in Humans

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Abstract

■ Cognitive flexibility allows us to adaptively switch between different responsibilities in important domains of our daily life. Previous work has elucidated the neurochemical basis underlying the ability to switch responses to a previously nonreinforced exemplar and to switch between attentional sets. However, the role of neuromodulators in task switching, the ability to rapidly switch between two or more cognitive tasks afforded by the same stimuli, is still poorly understood. We attempted to fill this gap by manipulating norepinephrine levels using stress manipulation (Study 1a, $n = 48$; between-group design), transcutaneous vagus nerve stimulation at two different intensities (Study 1b, $n = 48$; sham-controlled between-group design), and pharmacological manipulation (Study 2, $n = 24$; double-blind crossover design), all of which increased salivary cortisol measures. Participants repeatedly switched between two cognitive tasks (classifying a digit as high/low [Task 1] or as odd/even [Task 2]), depending on the preceding cue. On each trial, a cue indicated the task to be performed. The cue–stimulus interval was varied to manipulate the time to prepare for the switch. Participants showed typical switch costs, which decreased with the time available for preparation. None of the manipulations modulated the size of the switch costs or the preparation effect, as supported by frequentist and Bayesian model comparisons. Task-switching performance reflects a complex mix of cognitive control and bottom–up dynamics of task-set representations. Our findings suggest that norepinephrine does not affect either of these aspects of cognitive flexibility. ■

INTRODUCTION

Cognitive flexibility, the ability to learn associations between stimuli, actions, and outcomes and to quickly adapt ongoing behavior to salient changes in the environment, is very important for human survival (Kehagia, Murray, & Robbins, 2010). It allows us to "juggle" between different responsibilities in important domains of our daily life and allows species to face new and unexpected conditions in the environment, including threatening conditions (Cañas, Quesada, Antolí, & Fajardo, 2003). Cognitive flexibility is a multifaceted construct. Two examples of lower-order cognitive flexibility are basic reinforcement learning and reversal learning—responding to a previously nonreinforced exemplar within the same dimension. These cognitive functions are critically dependent on environmental signals or feedback, allowing us to flexibly learn and unlearn goal-directed behaviors (Kehagia et al., 2010). Two examples of higher-order cognitive flexibility are extradimensional attentional set shifting and task switching. Extradimensional set shifting concerns the ability to adapt behavior flexibly after feedback but pertains to broader stimulus dimensions rather than a specific exemplar. Task switching is a purer form of cognitive flexibility because it is uncontaminated by learning and feedback processing (Kehagia et al., 2010). Instead, people rely on implicit or explicit cues that indicate frequent shifts between two or more tasks afforded by the same stimuli, for example, to classify a digit as odd–even or as high–low with a left or right button press (Kiesel et al., 2010; Monsell & Mizon, 2006; Monsell, Sumner, & Waters, 2003).

Previous literature shows that neuromodulators such as dopamine, serotonin, and norepinephrine (NE) modulate several forms of cognitive flexibility. Dopamine modulation in the striatum and pFC is critical for basic reinforcement learning and the integration of negative feedback during reversal learning, whereas serotonin appears to play an important role in inhibiting perseverative responding after reversal of cue–outcome contingencies (Matias, Lottem, Dugué, & Mainen, 2017; Kehagia et al., 2010; Walker, Robbins, & Roberts, 2009). In contrast, NE plays a crucial role in extradimensional set shifting and adaptive updating of beliefs about the environment (Sales, Friston, Jones, Pickering, & Moran, 2019; Jepma et al., 2018; Pajkossy, Szõllõsi, Demeter, & Racsmány, 2018; Janitzky et al., 2015; Tait et al., 2007; Lapiz & Morilak, 2006). Building on such findings, Kehagia and colleagues (2009, 2010) proposed that NE may also be critical for task switching: flexibly shifting between task sets on the basis of trial-to-trial instruction cues. However, surprisingly little research has investigated the role of NE in task switching (Wolff, Mückschel,

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Ziemssen, & Beste, 2018; Steenbergen, Sellaro, de Rover, Hommel, & Colzato, 2015). Here, we addressed this question by examining task-switching performance after manipulating activity of the locus ceruleus (LC)-NE system using stress induction, transcutaneous vagus nerve stimulation (tVNS), and administration of the drug atomoxetine.

The relationship between stress and LC activation is well documented, and the LC is an important component of the central stress circuitry (for reviews, see Sara & Bouret, 2012; Itoi & Sugimoto, 2010; Aston-Jones, Valentino, Van Bockstaele, & Meyerson, 1994). Most environmental stressors increase the spontaneous discharge rate of the LC. Several brain areas involved in the typical stress response, including the central nucleus of the amygdala and paraventricular nucleus of the hypothalamus, provide inputs to the LC. Corticotropin-releasing hormone is an important mediator of this stress-induced LC activation and ensuing effects throughout the brain, which prepare the organism for a rapid and appropriate behavioral response to the stressor. Indeed, blockade of noradrenergic beta receptors diminishes the effect of stress on emotional memory (Kroes et al., 2016; Cahill & McGaugh, 1998) and global brain state (Hermans et al., 2011). In the present research, we used an effective, standardized protocol for experimental stress induction in humans (Schwabe & Schächinger, 2018).

The vagus nerve is the longest nerve in our body and communicates the state of the viscera to the brain and vice versa. Importantly, the vagus nerve projects to the nucleus tractus solitarius, which in turn projects directly and indirectly to the LC, the main source of NE in the brain (Berridge & Waterhouse, 2003). External stimulation of the vagus nerve (VNS, used usually to suppress epileptic seizures) can be achieved either invasively, with a surgical procedure involving vagus nerve stimulator implantation within the chest cavity, or transcutaneously, with an iPod-like device delivering electrical impulses to the auricular branch of the vagus nerve, which is situated close to the surface of the skin of the outer ear. Animal studies have found that VNS increased the firing rate of NE neurons in the LC (Raedt et al., 2011; Dorr & Debonnel, 2006; Roosevelt, Smith, Clough, Jensen, & Browning, 2006) and increased extracellular NE levels in pFC (Follesa et al., 2007), basolateral amygdala (Hassert, Miyashita, & Williams, 2004), and cerebrospinal fluid (Martlé et al., 2015). Importantly, this increase in NE levels occurred in a dose-dependent manner and returned to baseline after termination of VNS (Raedt et al., 2011; Roosevelt et al., 2006). Although there is no direct evidence that tVNS has similar effects on the LC-NE system, fMRI studies in healthy humans have demonstrated that tVNS elicits widespread changes in cortical and brainstem activity (Frangos, Ellrich, & Komisaruk, 2015; Kraus et al., 2007). Other recent work has shown that tVNS modulates hormonal (Warren et al., 2019; Ventura-Bort et al., 2018) and psychophysiological (Ventura-Bort et al., 2018; but see Warren et al., 2019) indices of noradrenergic function in human participants. In the current research, we examined the effects on cognitive flexibility of tVNS at two levels of intensity.

Although the abovementioned methods of tVNS and stress induction allow examination of NE effects on cognition, psychopharmacological manipulation provides a more robust method for directly manipulating NE levels and for establishing a causal role for NE. To this end, we also manipulated brain-wide NE levels via administration of the NE transporter blocker atomoxetine, a compound usually prescribed to treat attention-deficit hyperactivity disorder (Pringsheim, Hirsch, Gardner, & Gorman, 2015; Sharma & Couture, 2014). In cortical areas, the NE transporter is responsible for the reuptake of not only NE but also dopamine from the synaptic cleft (Devoto & Flore, 2006). Thus, atomoxetine increases both central NE and cortical dopamine levels (Koda et al., 2010; Bymaster et al., 2002). Finally, in human participants, atomoxetine administration has been shown to affect NE biomarkers such as alpha-amylase (Warren, van den Brink, Nieuwenhuis, & Bosch, 2017; Chamberlain, Müller, Cleary, Robbins, & Sahakian, 2007).

We studied higher-order cognitive flexibility using a task-switching paradigm (Monsell et al., 2003) in which the task to be performed on each trial was indicated by a cue presented at the start of the trial. This paradigm distinguishes between trials on which the task changes ("switch trials") and trials on which the task stays the same ("repeat trials"). The finding of interest is that RT is longer, and error rate is greater, on switch trials (the "switch cost"), and as the cue–stimulus interval (CSI) is prolonged—allowing more opportunity for advance preparation—the switch cost is reduced (the "preparation effect"). Switch costs are attributable to a combination of the time required for resolving interference from residual activation of the previous, no-longer-relevant task set ("task-set inertia") and of the time required for retrieving the newly cued task set ("task-set reconfiguration"; Monsell et al., 2003). The cognitive flexibility required to switch between tasks depends on the dynamic transformation of neural task-set representations from trial to trial (Qiao, Zhang, Chen, & Egner, 2017; Yeung, Nystrom, Aronson, & Cohen, 2006). To ensure that the observed switch costs and preparation effect would accurately reflect this type of cognitive flexibility instead of a cue-repetition effect, we used two cues per task, which allowed us to avoid direct cue repetitions between trials (Monsell & Mizon, 2006; Logan & Bundesen, 2003).

In Study 1, we tested three groups of participants. All participants performed the task on two separate occasions in which either tVNS or sham stimulation was applied according to a single-blind counterbalanced design. Two of the groups received common, medium-intensity (0.5-mA) tVNS. One of those groups underwent also a stress induction procedure; the other group underwent a control procedure. Comparison of those two groups allowed us to examine the effect of stress (in the context of tVNS) on task switching, as reported under the Results of Study 1a: Effects of tVNS and Stress section. The third group received tVNS (vs. sham) at a higher intensity (1.0 mA). Comparison of this group

with the medium-intensity/no-stress group allowed us to examine the relatively unknown dose-dependent effects of tVNS. This can be seen as an initial step toward establishing a linear or curvilinear relationship between tVNS intensity and cognitive flexibility or other aspects of cognitive task performance (Hulsey et al., 2017; Frangos et al., 2015; Dietrich et al., 2008; Ghacibeh, Shenker, Shenal, Uthman, & Heilman, 2006). These results are reported under the Results of Study 1b: Effects of tVNS Intensity section. In Study 2, we examined the effect of our psychopharmacological manipulation on task switching, using a double-blind placebo-controlled crossover design.

Note that we do not claim that stress induction, tVNS, and atomoxetine selectively affect NE levels. Stress causes a myriad of adaptive neurochemical changes. VNS can affect levels of dopamine and serotonin, although these effects may require chronic stimulation or reflect indirect effects of the change in NE levels (Martlé et al., 2015; Manta, El Mansari, Debonnel, & Blier, 2013). Furthermore, as mentioned above, atomoxetine also increases cortical dopamine levels. We also do not intend to suggest that the three manipulations affect the LC-NE system in a similar way. However, if task switching is crucially dependent on activity of the LC-NE system, one would expect effects of (some of) these manipulations on task-switching performance. To foreshadow the results, we did not find such effects.

STUDY 1

Methods

Participants

Seventy-two Dutch native-speaking volunteers (18–29 years old; mean age = 21.4 years) participated in this study. All had normal or corrected-to-normal vision. To avoid menstrual cycle effects on cortisol responses (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999), only male participants were included. Exclusion criteria were as follows: neurological or psychiatric disorder, bradycardia, cardiac arrhythmia, cardiovascular disease, psychoactive medication or drug use, active implants (e.g., cochlear implant), and skin disorder such as eczema. Participants were asked to refrain from alcohol intake within 24 hr before the study and to refrain from excessive exercise, caffeine, and heavy meals within 3 hr before the study. To ensure that the participants were blind to the active stimulation/sham condition, prior participation in other tVNS studies was an additional exclusion criterion. All participants gave written informed consent before their participation and, based on their preference, were compensated with 24 euros or course credits. The study was approved by the ethics committee of the Institute of Psychology, Leiden University.

Design

tVNS was applied according to a single-blind, sham-controlled, crossover design. The study consisted of two sessions, scheduled 1 week apart at the same time of the day. To control for circadian fluctuations in cortisol levels (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007), all sessions were conducted between 12:00 and 6:00 p.m. Participants received either tVNS or sham stimulation, in a counterbalanced order. Participants were randomly assigned to one of three groups (each with $n = 24$):

- Medium-intensity tVNS (0.5 mA)
- Medium-intensity tVNS (0.5 mA) and stress induction
- High-intensity tVNS (1.0 mA)

The study design and procedure were the same for all groups, with the following exceptions. The intensity of tVNS differed between the medium- and high-intensity groups. In addition, in the stress group, stress was induced using a socially evaluated cold pressor test (SECPT), whereas the other two groups received a control treatment that involved a similar procedure but without social, psychological, and physical stress induction (see below).

Task

Experimental phase. To assess cognitive flexibility, we used an unpredictable cued task-switching paradigm (Monsell et al., 2003), implemented in E-Prime (Psychology Software Tools). Participants were asked to classify a digit (1–4, 6–9) as high/low (Task 1) or as odd/even (Task 2), depending on the preceding cue. The cue was a colored circle (pink or yellow) or an outline shape (diamond or square; see Figure 1), displayed on a gray background. The diamond-shaped and pink-colored cues indicated that Task 1 should be performed, whereas the square-shaped and yellow-colored cues indicated that Task 2 should be performed. The probability of a task switch was 25%.

Digits were displayed in a black Courier New 24-point font with a height of 1 cm centered on the cue of side 3 cm, which was displayed in the center of the screen (Figure 1). Each trial started with a blank screen for 750 msec, followed by a fixation cross of 500 msec. After a preparation interval of 150 or 800 msec, the digit appeared in the center of the cue until the participant's response. A response triggered the immediate onset of the next trial, unless a wrong key was pressed, in which case an error message appeared for 2 sec to allow the participant to recover before onset of the next trial.

To unconfound the effects of task switching and cue change (Monsell & Mizon, 2006), the cue changed on every trial, alternating between shape and color. The CSI was manipulated in such a way that the participants had little time for advance preparation (CSI = 150 msec) or more time (CSI = 800 msec). Participants performed the tasks by pressing the letters "Q" (odd, high) or "P" (even, low) on a keyboard with their left and right index fingers. They were instructed to respond as quickly as possible while minimizing the number of errors and to use the available preparation time effectively.

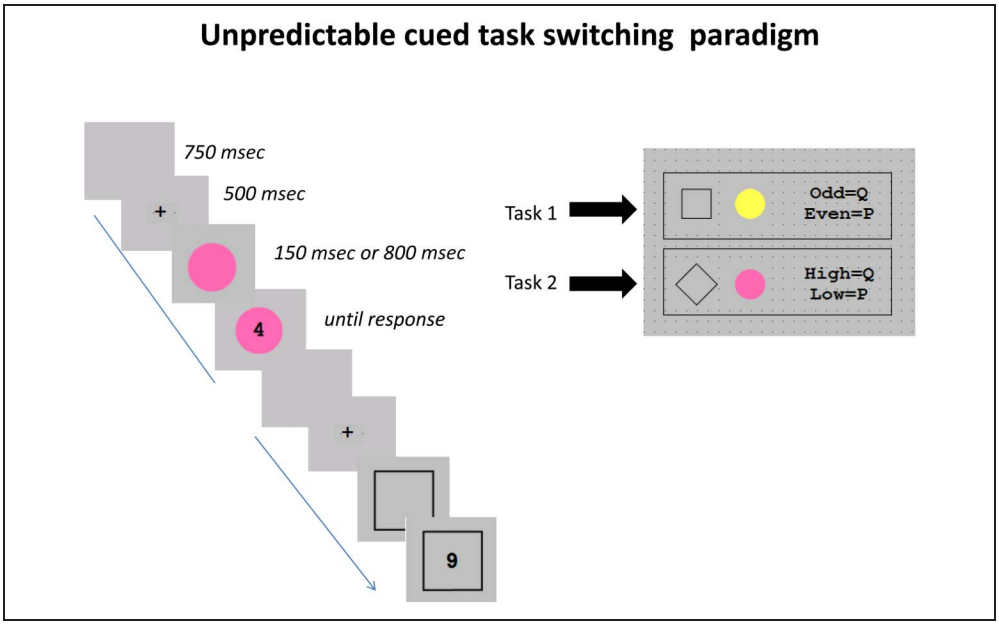

Figure 1. Illustration of the task-switching paradigm. The same paradigm was used in all the studies reported in this paper.

The experiment consisted of 768 trials that were presented in six blocks of 128 trials. Each block started with four warm-up trials and consisted of trials with only a long or short CSI. Blocks with long and short CSIs alternated in an ABABAB order for half of the participants and in a BABABA order for the other half of the participants. This factor was stratified with treatment order to ensure that the order of the CSIs across blocks was orthogonal to the order of treatments (tVNS/sham in the first session for Study 1 and placebo/atomoxetine in the first session for Study 2). In between the blocks, there were participant-paced breaks with a maximum duration of 15 sec, and at the end of each block, participants received written feedback about their mean RT and error rate for that block. Participants were challenged to beat this performance in the remaining blocks. The task-switching experiment lasted approximately 30 min.

Practice phase. Before the actual experiment, participants received extensive practice to ensure that they learnt the cue–stimulus mapping well. The practice task consisted of four blocks and lasted approximately 20 min. During the first block, participants learnt the first task by practicing 32 trials of the odd–even task with the digit displayed inside the appropriate cue. During the second block, participants practiced 32 trials of the high–low task, using the same procedure. In the third block, participants performed 64 trials with a long CSI and random switches between Task 1 and Task 2. The last block consisted of 64 trials with a short CSI and random switches between Task 1 and Task 2.

To ensure proper learning of the cue–task mapping, the cue–task mapping was displayed in the top-right corner of the screen throughout the practice phase. In addition, before the initiation of the third practice block, the experimenter ran through the learned tasks together with the participant, to make sure the cue–task mappings were properly represented. To mitigate learning effects, the practice phase of Session 2 was half as long as the practice phase of Session 1.

Data Analysis

We performed frequentist mixed ANOVAs with mean correct RT and accuracy (% errors) as dependent variables; treatment (tVNS/sham), CSI (150/800 msec), trial type (switch/repeat), and task (odd/even or high/low) as within-participant independent variables; and group (stress vs. no stress) and treatment order (Study 1a) or tVNS intensity (0.5/1.0 mA) and treatment order (Study 1b) as between-participant variables. Treatment order and Task were factors of no interest, so we do not report any statistical terms involving these factors. The following trials were excluded from the analyses: all practice trials, warm-up trials, trials after errors, and trials with RTs longer than 2 sec.

Data were analyzed with IBM SPSS Statistics for Windows, Version 25 (IBM Corp.). A significance level of $p < .05$ was adopted for all statistical tests. Significant results were followed by t tests to clarify the direction of the effect. Greenhouse–Geisser correction was used whenever the assumption of sphericity was violated.

We also performed Bayesian mixed ANOVAs of mean correct RTs in JASP (JASP Team, 2019). A strength of the Bayesian approach is that it enables us to quantify evidence for both the alternative and null hypotheses. In the Bayesian model comparisons, the null model included the main effects of CSI and trial type as well as their interaction. Alternative models also included effects of Treatment (tVNS/sham) and Group (stress vs. no stress; Study 1a), or Treatment and tVNS Intensity (0.5/1.0 mA), to examine the effects of these factors on switch costs and the preparation effect. Note that JASP obeys the principle of marginality,

meaning that models that feature an interaction also feature the constituent main effects (van den Bergh et al., 2020).

Procedure

The timeline of each experimental session is illustrated in Figure 2. The tVNS or sham stimulation started before the practice phase of the task-switching experiment. After the practice, which took about 20 min, the participants underwent an assessment of their mood. Then, the stress induction (or control procedure) took place, followed by the actual task-switching paradigm.

tVNS. We used a tVNS device to stimulate the vagus nerve (NEMOS, Cerbomed). The device was switched on for a period of 75 min, with a frequency of 25 Hz, and stimulation intensity was set at 0.5 mA for the medium-intensity group or 1.0 mA for the high-intensity group. The stimulation followed a pattern set by the manufacturer, alternating between 30 sec on and 30 sec off. In one of the sessions, the participant received tVNS on the left concha, at the inner side of the ear where the afferent auricular branch of the vagus nerve can be stimulated. In the other session, participants received sham stimulation on the left ear lobe. Administering sham stimulation in this manner has proven to produce no significant activation in the brainstem and cortex (Kraus et al., 2013).

At the end of each session, an aftereffect questionnaire was used to assess possible side effects of tVNS and how the participants experienced the stimulation (Sellaro et al., 2015). The participants were asked to indicate on a 5-point scale the extent to which specific possible tVNS side effects/experiences applied to them. The included complaints were as follows: headache, neck pain, uncomfortable feeling, nausea, muscle constructions, tingling sensation, burning feeling under electrodes, and open-question "other" where participants could mention complains missing from the list.

Mean ratings of uncomfortable feeling were 2.0 for the 0.5-mA group (sham: 1.6) versus 2.1 for the 1.0-mA group (sham: 1.7) and 1.9 (sham: 1.9) for the stress group. Scores for tingling feeling were 2.7 for the 0.5-mA group (sham: 2.4) versus 3.1 for the 1.0-mA group (sham: 3.4) and 3.1 for the stress group (sham: 2.1). Finally, scores of feeling of burning sensation were 2.3 for the 1.0-mA group (sham: 1.7) but below 2.0 for the other groups. Ratings for other scales were all below 2.0.

Stress induction. To manipulate stress, we used the SECPT, which combines induction of physiological (cold pressor) and psychological (negative social evaluation) stress. The SECPT has been shown to be a robust stressor, leading to increased levels of the stress hormone cortisol (Schwabe, Haddad, & Schächinger, 2008).

The participant was instructed to submerge his right hand until the wrist into a bucket of ice water (4°C), to not move this hand, and to keep it in the water until he could not bear it anymore. Although no time restriction was revealed to the participant, in line with ethical and safety restrictions, he was told by the experimenter to take his hand out of the water after 3 min. To ensure induction of psychological stress, instructions were given in a strict manner by an experimenter who was wearing a white coat, and the participant was evaluated by a committee of two members while having his hand in cold water. The evaluation included visual observation, mock notes, and negative feedback by the committee members and simultaneous videotaping of the participant. The participant was told that the camera was recording his facial expressions, which would be evaluated at a later time point.

In the control condition, the same procedure was followed but the participant submerged his hand in room temperature water (22–25°C) and the evaluators did not induce any psychological/social stress. To be consistent, the same instructions were given to the participant as during the stress manipulation but not in a strict manner. Although the participant was told to keep his hand in the water until he could not bear it anymore and no time restriction was revealed to him, the experimenter asked him to take his hand out of the water when the 3 min had passed. Throughout the control condition, the control social evaluators avoided looking at the participant and acted in a neutral manner. Also, it was clear that the camera that was in the room was turned off and pointing toward the wall instead of the participant.

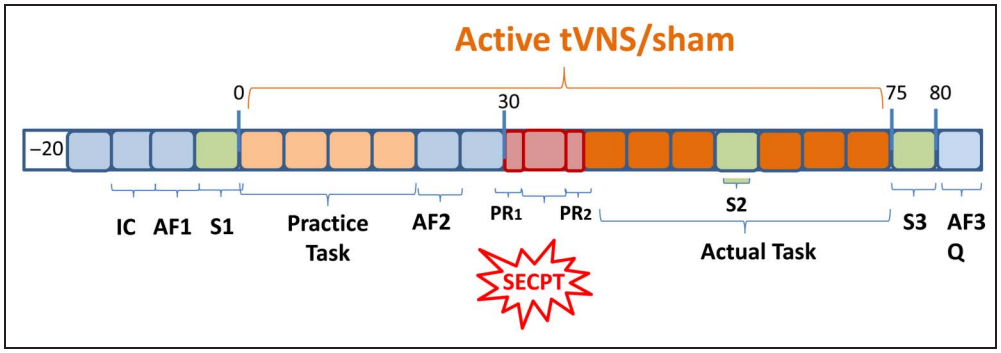

Figure 2. Timeline of procedures in Study 1. Each square represents a 5-min period. IC = informed consent; S(1, 2, 3) = saliva measurement; AF(1, 2, 3) = Affect Grid; PR(1, 2) = pain rating; Q = aftereffect questionnaire.

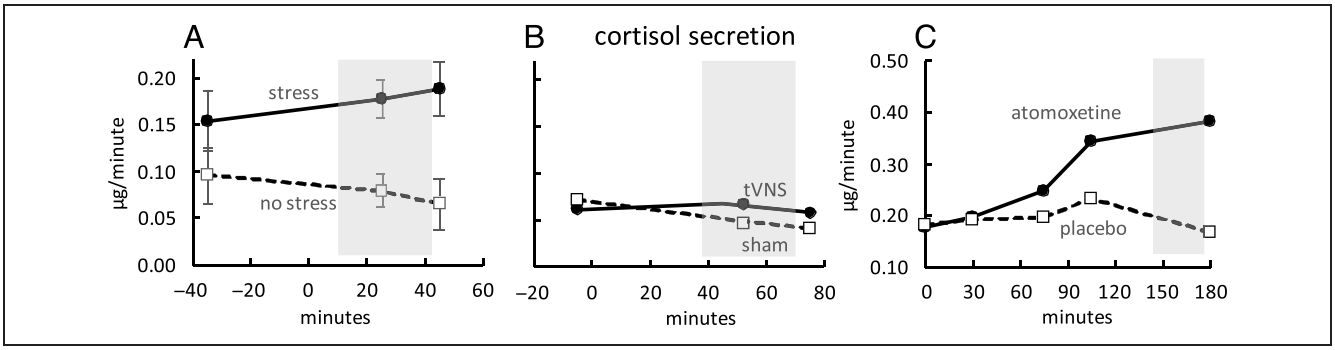

Figure 3. Effects of stress, tVNS (Warren et al., 2019), and atomoxetine (Warren, van den Brink, et al., 2017) on salivary cortisol secretion. Error bars reflecting *SEM* are shown for the between-group comparison (stress vs. no-stress). $t = 0$ min reflects the onset of stress induction, the start of tVNS, and the moment of pill administration. Gray-shaded bars reflect the time window of the task-switching experiment.

Validation of stress manipulation. To test the effectiveness of the stress manipulation, we assessed psychological and physiological distress by means of subjective pain ratings and salivary cortisol levels. Pain ratings were collected immediately before and after the stress induction. Participants indicated on a visual scale ranging from 0 to 100 how much pain they felt at the moment. Changes in pain perception were assessed by subtracting the values reported after the SECPT/control manipulation from those reported immediately before. The difference values for the stress and nonstress group were compared using independent t tests.

To assess cortisol levels, saliva samples were collected at three time points (see Figure 2): at baseline, soon after the stress or control manipulation, and after completion of the task. Samples were assayed for cortisol using a competitive enzyme-linked immunosorbent assay, according to the manufacturer's instructions (IBL). All samples of a given participant were assayed simultaneously (for additional information about saliva sample collection and processing methods, see Warren et al., 2019; Warren, van den Brink, et al., 2017). We calculated salivary cortisol secretion as the flow rate multiplied by the concentration values, as in our previous work (Warren et al., 2019; Warren, van den Brink, et al., 2017) and as is considered the "gold standard" in the field. Cortisol secretion data were analyzed using a 3 × 2 × 2 mixed ANOVA with Time Point (first vs. second vs. third measurement) and Treatment (tVNS vs. sham) as within-participant factors and Group (stress vs. no stress) as a between-participant factor.

Results of Study 1a: Effects of tVNS and Stress

Effects of Stress on Subjective Pain and Salivary Cortisol

Stress led to increased pain perception and elevated salivary cortisol levels. Exposure to the SECPT increased mean subjective pain ratings (stress group: 29.65, no-stress group: 3.79), $t(32) = 7.94, p < .001$. Twenty-three participants in the no-stress group and 20 participants in the stress group provided cortisol samples with concentrations within the sensitivity range of our assay in all six cells of the design (3 Time Points × 2 Treatment conditions). As shown in Figure 3, the stress induction procedure increased cortisol secretion levels, as compared to the control procedure, yielding a significant main effect of Group, $F(1, 41) = 7.55$, $p = .009$, $\eta_p^2 = .16$, and a marginally significant Time Point × Group interaction, $F(2, 82) = 3.00$, $p = .06$, $\eta_p^2 = .07$ (after Greenhouse–Geisser correction). Whereas cortisol secretion levels did not differ between the groups at baseline, $F(1, 41) = 1.67$, $p = .20$, $\eta_p^2 = .04$, cortisol levels were significantly higher in the stress group at 15 min, $F(1, 41) = 13.84$, $p = .001$, $\eta_p^2 = .25$, and 70 min after the end of stress induction, $F(1, 41) = 9.78$, $p = .003$, $\eta_p^2 = .19$.

RTs

Mean RTs are presented in Figure 4; and switch costs, in Figure 5. Participants showed a typical switch cost of 60 msec, $F(1, 44) = 39.8$, $p < .001$, $\eta_p^2 = .48$ (switch: 786 msec, repeat: 726 msec), which decreased with the time available for preparation, $F(1, 44) = 14.45$, $p < .001$, $\eta_p^2 = .25$. The switch cost was smaller in long-CSI blocks (39 msec) than in short-CSI blocks (79 msec). There was also a main effect of CSI, $F(1, 44) = 160$, $p < .001$, $\eta_p^2 = .78$. These are well-established findings in task-switching research.

Treatment, $F(1, 44) < 1$, $p = .97$, $\eta_p^2 < .001$, and Group, $F(1, 44) < 1$, $p = .73$, $\eta_p^2 = .97$, did not have a main effect on RT (stress: 749 msec, no stress: 763 msec), and there was no significant interaction between Treatment and Group, $F(1, 44) = 0.24$, $p = .62$, $\eta_p^2 = .006$. Importantly, the switch cost and the preparation effect were not modulated by tVNS, $F(1, 44) = 1.55$, $p = .22$, $\eta_p^2 = .034$, and $F(1, 44) = 3.19$, $p = .08$, $\eta_p^2 = .068$, respectively, or Group, $F(1, 44) = 2.39$, $p = .13$, $\eta_p^2 = .05$, and $F(1, 44) = 1.19$, $p = .28$, $\eta_p^2 = .026$, respectively, and there were no interactions between those factors and other factors of interest.

Accuracy

Percentages of errors are presented in Figure 4; and switch costs, in Figure 5. Participants showed a typical switch cost of 4.2%, $F(1, 44) = 67.23$, $p < .001$, $\eta_p^2 = .604$ (switch: 91.2%, repeat: 95.4%), which decreased with the time

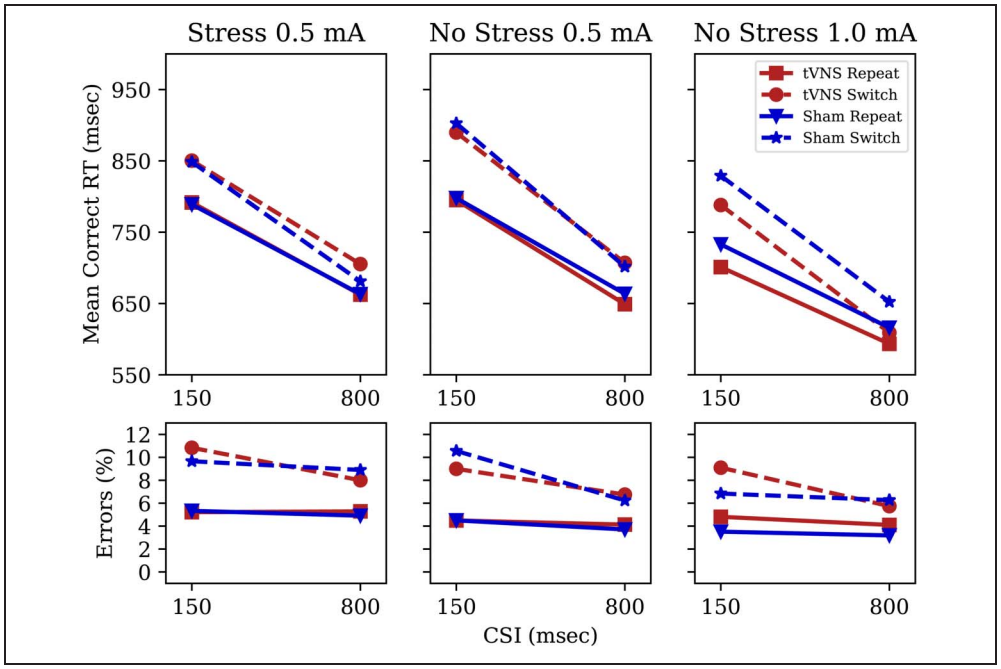

Figure 4. Mean correct RT (top) and error rate (bottom) as a function of group, treatment (tVNS vs. sham), CSI, and trial type.

available for preparation, $F(1, 44) = 12.75, p = .001, \eta_p^2 = .225$. The switch cost was smaller in long-CSI blocks (3.1%) than in short-CSI blocks (5.1%). There was also a main effect of CSI, $F(1, 44) = 17.25, p < .001, \eta_p^2 = .282$.

Treatment, $F(1, 44) < 1, p = .97, \eta_p^2 < .001$, and Group, $F(1, 44) = 0.50, p = .48, \eta_p^2 = .011$, did not have a main effect on accuracy. There was no significant interaction between Treatment and Group, $F(1, 44) < 1, p = .67, \eta_p^2 = .004$. The switch cost and the preparation effect were not modulated by tVNS, $F(1, 44) < 1, p = .58, \eta_p^2 = .007$, and $F(1, 44) < 1, p = .71, \eta_p^2 = .003$, respectively, or Group, $F(1, 44) < 1, p = .82, \eta_p^2 = .001$, and $F(1, 44) < 1, p = .41, \eta_p^2 = .015$, respectively, and there were no interactions between these factors and other factors of interest.

Exploratory Analysis: Effect of Stress in Sham Condition Only

It is possible that stress did not affect task-switching performance because it was manipulated in the context of tVNS—

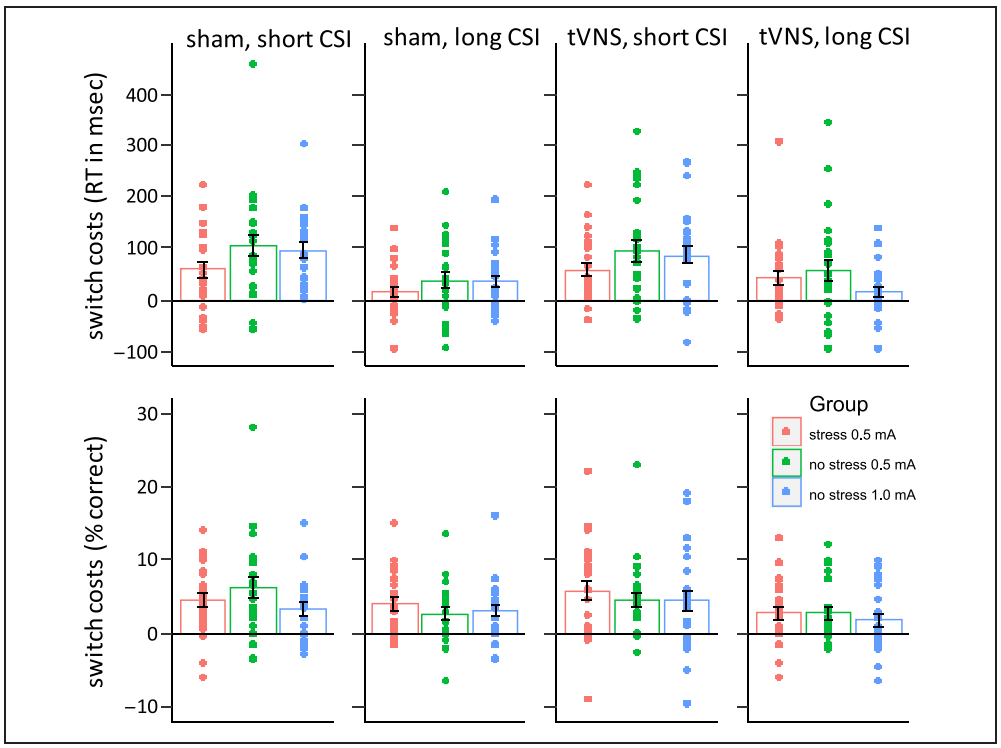

Figure 5. Switch costs (top: RT; bottom: accuracy) for each of the three groups as a function of treatment (tVNS vs. sham) and CSI. Error bars denote *SEM*. Dots reflect the switch costs of each individual in the group.

perhaps tVNS somehow suppressed the effect of stress (Lerman et al., 2019; Tobaldini et al., 2019). To examine this scenario, we carried out an ANOVA comparing the stress and nonstress groups (0.5 mV), including only data from the sham condition. With regard to RT, Group did not have a main effect, $F(1, 44) < 1, p = .59, \eta_p^2 = .007$, and did not modulate the switch cost, $F(1, 44) = 2.75, p = .10, \eta_p^2 = .059$, and the preparation effect, $F(1, 44) < 1, p = .33, \eta_p^2 = .022$. Similarly, with regard to accuracy, Group did not have a main effect, $F(1, 44) = 0.37, p = .55, \eta_p^2 = .008$, and did not modulate the switch cost, $F(1, 44) < 1, p = .89, \eta_p^2 < .001$, or the preparation effect, $F(1, 44) = 3.38, p = .07, \eta_p^2 = .071$. The latter p value reflects a trend toward a reduced preparation effect on accuracy in the stress condition. There was a significant Group × CSI interaction, $F(1, 44) = 4.65, p = .037, \eta_p^2 = .214$, with the effect of CSI on overall accuracy (i.e., regardless of trial type) being smaller in the stress group (mean = 0.6%) than in the nonstress group (mean = 1.8%). This result was driven by a difference in accuracy at the long CSI. Interpretations of this finding must remain tentative, given the post hoc nature of this analysis, the large number of statistical tests performed in the present studies, and the fact that the RT data did not show a similar interaction.

Bayesian ANOVA

A Bayesian ANOVA indicated that the null model, which only included main effects of CSI and trial type, as well as their interaction, outperformed models that included an effect of group or treatment on the switch cost (Treatment/Group × Trial Type) or the preparation effect (Treatment/Group × Trial Type × CSI; Table 1A). For example, the data were 7.2 and 66.8 times more likely under the null hypothesis than under models that also included an interaction between trial type and group or treatment, respectively. Thus, the Bayesian model comparisons provided "moderate" and "strong" evidence (Jeffreys, 1961) against an effect of stress or tVNS on the switch cost.

Results of Study 1b: Effects of tVNS Intensity

Effects of tVNS on Mood

Elsewhere, we report that, for a subset of the participants in this study, from whom we collected and analyzed saliva measurements, tVNS treatment (0.5 mA) significantly increased salivary levels of cortisol and α-amylase compared to sham stimulation (Warren et al., 2019), thus confirming the effect of tVNS. The cortisol secretion results from that study are replotted in Figure 3. Here, based on preliminary results suggesting that chronic tVNS can benefit aspects of mood in older adults (Bretherton et al., 2019), we explored whether a brief period of tVNS would affect mood in our young adult participants. Mood was assessed at three time points (Figure 2) using the Affect Grid (Russell, Weiss, & Mendelsohn, 1989), a quick means of assessing affect along the dimensions of pleasure–displeasure and arousal–sleepiness. Pleasure and arousal scores were analyzed separately by means of repeated-measures ANOVAs with Time Point (first vs. second vs. third measurement) and Treatment (tVNS vs. sham) as within-participant factors and tVNS Intensity (0.5/1.0 mA) and Treatment order as between-participant factors. There was an effect of Time Point on pleasure, $F(2, 88) = 7.77, p = .001, \eta_p^2 = .150$, with pleasure decreasing over time, but there was no effect of Treatment or tVNS Intensity on arousal, $F(1, 44) = 1.78, p = .19, \eta_p^2 = .039$, and $F(1, 44) = 0.44, p = .51, \eta_p^2 = .010$, respectively, and pleasure, $F(1, 44) = 0.27, p = .60, \eta_p^2 = .006$, and $F(1, 44) = 0.006, p = .94, \eta_p^2 < .001$, respectively.

Table 1A. Bayesian Model Comparisons for a Selection of Theoretically Relevant Models in Study 1a

Null Model	*Main Effect of Group or Treatment*	*Two-way Interactions Including Group (Stress vs. No-stress) or Treatment (tVNS/Sham)*	*Three-way Interactions Including Group (Stress vs. No-stress) or Treatment (tVNS/Sham)*	BF_{01}
Trial Type + CSI + Trial Type × CSI				1.0
Trial Type + CSI + Trial Type × CSI	+ Group			2.7
Trial Type + CSI + Trial Type × CSI	+ Group	+ Group × Trial Type		7.2
Trial Type + CSI + Trial Type × CSI	+ Group	+ Group × Trial Type + Group × CSI	+ Group × Trial Type × CSI	98.3
Trial Type + CSI + Trial Type × CSI	+ Treatment			11.3
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × Trial Type		66.8
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × Trial Type + Treatment × CSI	+ Treatment × Trial Type × CSI	1532.4

The first four columns show the predictors included in each model. The BF_{01} column shows the Bayes factors of all models compared to the null model. Bayes factors larger than 1.00 mean that the correct RT data were more likely under the null model than under the alternative model.

RTs

Mean RTs are presented in Figure 4; and switch costs, in Figure 5. Participants showed a typical switch cost of 66 msec, $F(1, 44) = 49.5, p < .001, \eta_p^2 = .529$ (switch: 760 msec, repeat: 694 msec), which decreased with the time available for preparation, $F(1, 44) = 35.7, p < .001, \eta_p^2 = .448$. The switch cost was smaller in long-CSI blocks (37 msec) than in short-CSI blocks (96 msec). There was also a main effect of CSI, $F(1, 44) = 177.4, p < .001, \eta_p^2 = .801$.

Treatment, $F(1, 44) = 2.8, p = .10, \eta_p^2 = .059$, and tVNS Intensity, $F(1, 44) = 3.2, p = .08, \eta_p^2 = .069$, did not have a main effect on RT, but the means indicated faster responses for the high-intensity group (0.5 mA: 763 msec, 1.0 mA: 690 msec). There was no significant interaction between Treatment and tVNS Intensity, $F(1, 44) = 1.3, p = .25, \eta_p^2 = .030$. Importantly, the switch costs and the preparation effect were not modulated by treatment, $F(1, 44) = 0.47, p = .50, \eta_p^2 = .011$, and $F(1, 44) = 0.35, p = .55, \eta_p^2 = .008$, respectively, or tVNS intensity, $F(1, 44) = 0.64, p = .43, \eta_p^2 = .014$, and $F(1, 44) = 0.50, p = .48, \eta_p^2 = .011$, respectively, and there were no interactions between these factors and other factors of interest.

Accuracy

Participants' accuracy scores (Figure 4) showed a typical switch cost of 3.5%, $F(1, 44) = 50.43, p < .001, \eta_p^2 = .534$ (switch: 92.5%, repeat: 96.0%), which decreased with the time available for preparation, $F(1, 44) = 15.12, p < .001, \eta_p^2 = .256$. The switch cost was smaller in long-CSI blocks (2.5%) than in short-CSI blocks (4.6%). There was also a main effect of CSI, $F(1, 44) = 24.53, p < .001, \eta_p^2 = .358$. Treatment, $F(1, 44) = 1.60, p = .21, \eta_p^2 = .035$, and tVNS Intensity, $F(1, 44) = 0.46, p = .50, \eta_p^2 = .010$, did not have a significant main effect on accuracy. Finally, there was no significant interaction between Treatment and tVNS Intensity, $F(1, 44) < 2.87, p = .10, \eta_p^2 = .061$.

Exploratory Analysis: tVNS at 1.0-mA Intensity Causes Speed–Accuracy Tradeoff

Although the omnibus ANOVA did not yield significant main effects of treatment and tVNS intensity, the right panel of Figure 4 suggests that tVNS at 1.0-mA intensity decreased RTs at the expense of more errors. To examine the robustness of this finding, we carried out an ANOVA that included only the 1.0-mA group. Although high-intensity tVNS did not affect the switch cost and the preparation effect, $F(1, 22) = 1.89, p = .18, \eta_p^2 = .079$, and $F(1, 22) < 1, p = .55, \eta_p^2 = .017$, respectively, it had a main effect on RT, $F(1, 22) = 5.30, p = .03, \eta_p^2 = .194$, indicating that overall responses were faster in the tVNS condition (673 msec) than in the sham condition (708 msec).

Regarding accuracy, although high-intensity tVNS did not affect the switch cost, $F(1, 22) < 1, p = .79, \eta_p^2 = .003$, and the preparation effect, $F(1, 22) < 1, p = .35, \eta_p^2 = .040$, it had a main effect on error rate, $F(1, 22) = 5.16, p = .03, \eta_p^2 = .190$, indicating an overall decrease in accuracy in the tVNS condition (94.1%) compared to the sham condition (95.1%). For completeness, we report a significant two-way interaction between tVNS intensity and CSI, $F(1, 22) = 5.56, p = .03, \eta_p^2 = .202$, but that interaction was largely driven by a spurious difference in the effect of CSI between low and high sham stimulation intensity. Together, these findings suggest that tVNS at 1.0 mA caused a change in the participants' speed–accuracy tradeoff.

Table 1B. Bayesian Model Comparisons for a Selection of Theoretically Relevant Models in Study 1b

Null Model	*Main Effect of Intensity or Treatment*	*Two-way Interactions Including tVNS Intensity or Treatment (tVNS/Sham)*	*Three-way Interactions Including tVNS Intensity and/or Treatment (tVNS/Sham)*	BF_{01}
Trial Type + CSI + Trial Type × CSI				1.0
Trial Type + CSI + Trial Type × CSI	+ Intensity			0.8
Trial Type + CSI + Trial Type × CSI	+ Intensity	+ Intensity × Trial Type		3.8
Trial Type + CSI + Trial Type × CSI	+ Intensity	+ Intensity × Trial Type + Intensity × CSI	+ Intensity × Trial Type × CSI	73.1
Trial Type + CSI + Trial Type × CSI	+ Treatment			1.3
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × Trial Type		9.4
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × Trial Type + Treatment × CSI	+ Treatment × Trial Type × CSI	232.2
Trial Type + CSI + Trial Type × CSI	+ Intensity + Treatment	+ Intensity × Trial Type + Treatment × Trial Type + Intensity × Treatment	+ Intensity × Treatment × Trial Type	464.5

Bayesian ANOVA

As shown in Table 1B, the best-performing model in the Bayesian model comparisons was the model that included a main effect of intensity ($BF_{01} = 0.8$), consistent with our observation that tVNS at 1.0-mA intensity decreased RTs. Furthermore, the results showed moderate evidence (Jeffreys, 1961) for the null model relative to models that included an effect of treatment (tVNS vs. sham) or tVNS intensity on the switch cost and very strong and decisive evidence for the null model relative to models that included, respectively, an effect of treatment or tVNS intensity on the preparation effect. The analyses also yielded decisive evidence against an interaction effect of tVNS/sham and tVNS intensity on the switch cost.

STUDY 2: EFFECTS OF ATOMOXETINE

Methods

Participants

Twenty-four young volunteers (six men; 18–25 years old, mean age = 21.7 years) participated as part of a larger pharmacological neuroimaging study (van den Brink et al., 2016). Participants were screened by a physician for the following exclusion criteria: standard contraindications for MRI, current use of psychoactive or cardiovascular medication, a history of psychiatric illness or head trauma, cardiovascular disease, renal failure, hepatic insufficiency, glaucoma, hypertension, drug or alcohol abuse, learning disabilities, poor eyesight (myopia ≤ -6 diopters), smoking > 5 cigarettes a day, and pregnancy. All participants gave written informed consent before their participation and were compensated with €135. The study was approved by the Leiden University medical ethics committee.

Design and Procedure

The task performed by participants was identical to that used in Study 1. As in Study 1, blocks with long and short CSIs alternated in an ABABAB or BABABA fashion, and this between-participant factor was stratified with treatment order. The study was conducted according to a double-blind placebo-controlled crossover design. In each of the two sessions, scheduled 1 week apart at the same time of the day, participants received either a single oral dose of atomoxetine (40 mg) or placebo (125 mg of lactose monohydrate with 1% magnesium stearate, visually identical to the drug), in counterbalanced order. Data reported elsewhere (and replotted in Figure 3) show that, for these participants, the atomoxetine treatment significantly increased salivary levels of cortisol and α-amylase, reliable markers of sympathetic nervous system and hypothalamus–pituitary–adrenal axis activation, respectively (Warren, van den Brink, et al., 2017).

The practice of the task-switching paradigm started immediately after the pill ingestion and lasted 20 min, when the drug did not have any effects yet (Warren, Wilson, et al., 2017). The actual experiment was conducted when atomoxetine plasma levels were at their peak (t = 140–170 min; Sauer, Ring, & Witcher, 2005). Between the practice phase and the experimental phase, participants underwent resting-state functional neuroimaging.

Analysis

We performed frequentist mixed ANOVAs with Correct RT and Accuracy (% errors) as dependent variables; Treatment (atomoxetine/placebo), CSI (150/800 msec), Trial Type (switch/repeat), and Task (odd/even or high/low) as within-participant independent variables; and Treatment Order as a between-participant variable. As in Study 1, Treatment order and Task were factors of no interest, so we do not report any statistical terms involving these factors. Trial exclusion criteria were the same as in Study 1. In addition, we performed a Bayesian mixed ANOVA of mean correct RTs, using the same null model as in Studies 1a and 1b.

Results

RTs

Mean RTs are presented in Figure 6; and switch costs, in Figure 7. The pattern of findings was similar to that in Study 1. Participants showed a typical switch cost of 85 msec, $F(1, 22) = 47.21, p < .001, \eta_p^2 = .682$ (switch: 733 msec, repeat: 818 msec), which decreased with the time available for preparation, $F(1, 22) = 24.68, p < .001, \eta_p^2 = .529$. The switch cost was smaller in long-CSI blocks (44 msec) than

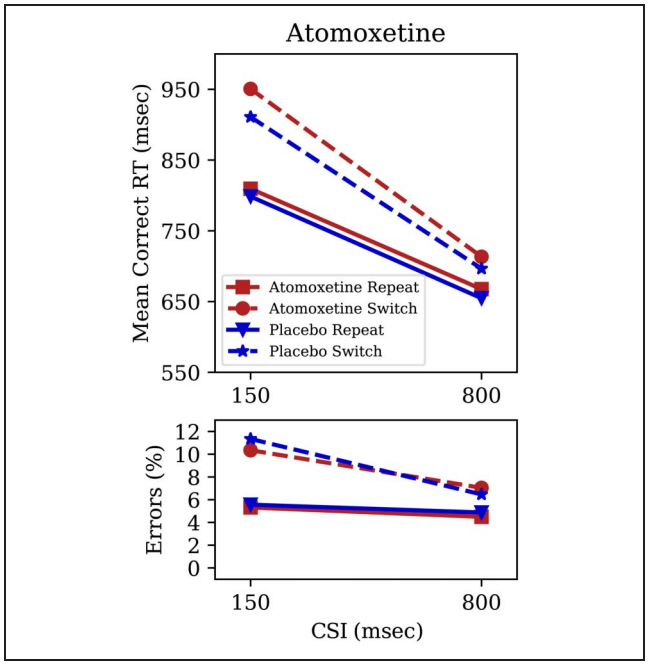

Figure 6. Mean correct RT (top) and error rate (bottom) as a function of treatment (atomoxetine, placebo), CSI, and trial type.

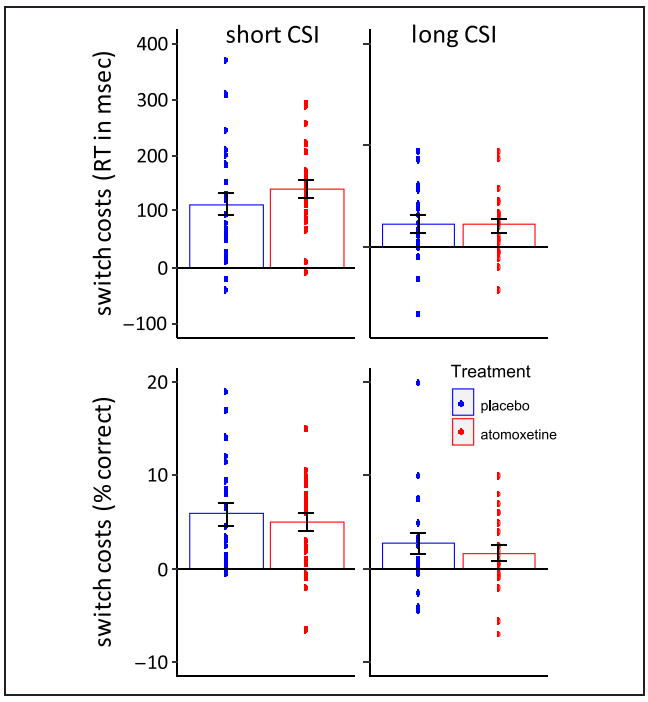

Figure 7. Switch costs (top: RT; bottom: accuracy) for placebo and atomoxetine as a function of CSI. Error bars denote *SEM*. Dots reflect the switch costs of each individual in each treatment.

in short-CSI blocks (127 msec). There was also a main effect of CSI, $F(1, 22) = 128.63$, $p < .001$, $\eta_p^2 = .854$.

Treatment, $F(1, 22) = 1.24$, $p = .27$, $\eta_p^2 = .053$, did not have a main effect on RT, but the means indicated somewhat slower responses in the atomoxetine condition (785 msec) than in the placebo condition (765 msec). Importantly, the switch costs, $F(1, 22) = 2.90$, $p = .10$, $\eta_p^2 = .116$, and the preparation effect, $F(1, 22) = 1.961$, $p = .18$, $\eta_p^2 = .082$, were not modulated by atomoxetine, and there were no interactions between Treatment and other factors of interest.

Accuracy

As shown in Figures 6 and 7, the pattern of mean accuracy scores was also similar to that in Study 1. Participants showed a typical switch cost of 3.8%, $F(1, 22) = 49.8$, $p < .001$, $\eta_p^2 = .693$ (switch: 91.2%, repeat: 95.0%), which decreased with the time available for preparation, $F(1, 22) = 9.8$, $p = .005$, $\eta_p^2 = .309$. The switch cost was smaller in long-CSI blocks (2.1%) than in short-CSI blocks (5.4%). There was also a main effect of CSI, $F(1, 22) = 17.9$, $p < .001$, $\eta_p^2 = .449$.

Treatment, $F(1, 22) < 1$, $p = .78$, $\eta_p^2 = .004$, did not have a main effect on Accuracy (atomoxetine: 93.2%, placebo: 93.0%). Importantly, the switch costs, $F(1, 22) < 1$, $p = .92$, $\eta_p^2 < .001$, and the preparation effect, $F(1, 22) < 1$, $p = .41$, $\eta_p^2 = .030$, were not modulated by atomoxetine, and there were no interactions between Treatment and other factors of interest.

Bayesian ANOVA

Bayesian model comparisons, summarized in Table 2, indicated that the data were 10.5 times more likely under the null model than under an alternative model in which atomoxetine affected the switch cost and 142.9 times more likely under the null model than under an alternative model in which atomoxetine affected the preparation effect. These results provide strong and decisive evidence (Jeffreys, 1961) against an effect of atomoxetine on the ability to switch between tasks.

GENERAL DISCUSSION

Previous work has suggested an important role for the LC-NE system in modulating several forms of cognitive flexibility, possibly by global modulation of gain and corresponding levels of decision noise (Kane et al., 2017; Warren, Wilson, et al., 2017; Aston-Jones & Cohen, 2005). However, it is

Table 2. Bayesian Model Comparisons for a Selection of Theoretically Relevant Models in Study 2

Null Model	*Main Effect of Treatment*	*Two-way Interactions Including Treatment (Atomoxetine vs. Placebo)*	*Three-way Interaction Including Treatment (Atomoxetine vs. Placebo)*	BF_{01}
Trial Type + CSI + Trial Type × CSI				1.0
Trial Type + CSI + Trial Type × CSI	+ Treatment			2.7
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × Trial Type		10.5
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × CSI		8.1
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × Trial Type + Treatment × CSI		45.5
Trial Type + CSI + Trial Type × CSI	+ Treatment	+ Treatment × Trial Type + Treatment × CSI	+ Treatment × Trial Type × CSI	142.9

The first four columns show the predictors included in each model. The BF_{01} column shows the Bayes factors of all models compared to the null model. Bayes factors larger than 1.00 mean that the correct RT data were more likely under the null model than under the alternative model.

still unknown whether NE levels are also critical for task switching (Kehagia et al., 2010; Kehagia, Cools, Barker, & Robbins, 2009), which requires the dynamic transformation of task-set representations from trial to trial. We addressed this question by examining cued task-switching performance after manipulating activity of the LC-NE system using stress induction, tVNS, and administration of atomoxetine. Our findings were highly consistent: None of these manipulations affected measures of task-switching performance (Figures 4–7), suggesting that NE is not involved in the cognitive flexibility required to switch between relatively abstract rules and sets of stimulus–response mappings.

A potential explanation for these findings is that our manipulations of the noradrenergic system were unsuccessful. However, this explanation is implausible. First, we used an effective, standardized protocol for experimental stress induction (Schwabe & Schächinger, 2018), which led to elevated salivary cortisol secretion levels in our participants (Figure 3). Furthermore, as argued above, the relationship between stress and noradrenergic activity has been well documented. The success of our tVNS manipulation is less clear. Invasive VNS in rodents results in increased NE levels. Elsewhere, we report that our 0.5-mA tVNS manipulation significantly increased salivary cortisol (Figure 3) and α-amylase, two indirect hormonal markers of noradrenergic function, in a partially overlapping group of participants (Warren et al., 2019). However, reported effects of tVNS on psychophysiological markers of noradrenergic function in humans (pupil size and P3 amplitude) are mixed (Warren et al., 2019; Ventura-Bort et al., 2018), perhaps because of differences in stimulation intensity or choice of sham stimulation location. It is also worth noting that our tVNS manipulation did not affect self-reported arousal levels as assessed with an affect grid questionnaire; this dissociation between subjective (psychological) and physiological arousal/stress levels has been reported in prior literature (Kindt, Soeter, & Vervliet, 2009). Finally, there is a wealth of evidence that atomoxetine has dose-dependent effects on LC firing rate and synaptic NE levels (Bari & Aston-Jones, 2013), and we reported data obtained in the same study and participants, showing that our manipulation increased salivary cortisol (Figure 3) and α-amylase (Warren, van den Brink, et al., 2017). Taken together, there is little doubt that at least two of our manipulations were successful at manipulating noradrenergic activity.

What do our null findings mean? The two tasks our participants had to perform involved the same inputs (digits 1–4 and 6–9) and outputs (keys Q and P) but differed in the mappings from input to output. The difficulty of combining these tasks lies in the brain's propensity to use the same representations for different purposes. That is, although in general this "multiplexing" offers an efficient way of encoding information, mutual interference, or cross-talk, arises when two tasks make simultaneous demands on the same representations (Feng, Schwemmer, Gershman, & Cohen, 2014). In principle, task switching is different from multitasking, in that the two sets of stimulus–response rules need not be active at the same time. However, it takes long for an irrelevant task-set representation to dissipate. In a typical, fast-paced task-switching experiment, this task-set inertia causes interference between the relevant and irrelevant task sets (Yeung et al., 2006; Monsell et al., 2003), which is reflected in the switch cost (i.e., a main effect of trial type). In such circumstances, cognitive control can be used to reduce cross-talk in the service of overall task performance (Feng et al., 2014). In a task-switching experiment, participants can—to some extent—actively prepare for the upcoming switch trial by proactively reconfiguring the task set. This process is reflected in the preparation effect—the reduction of switch costs with a growing CSI (i.e., an interaction between CSI and trial type). Importantly, the present findings suggest that our manipulations affected neither task-set inertia nor proactive task-set reconfiguration.

We are aware of two published studies on the effect of acute stress on task switching, which produced mixed results. Steinhauser and colleagues found that stress modulated the preparation effect (for RTs, not error rates), but not the switch costs itself (Steinhauser, Maier, & Hübner, 2007). Their control group showed the typical reduction in switch costs at a long CSI, but their stress group did not, which led the authors to conclude that stress induces a change in task-set reconfiguration strategy. In line with this finding, we found a trend toward a reduced preparation effect on accuracy (not RTs) in the stress group, but only if the analysis was constrained to the sham stimulation condition. Plessow and colleagues, using the same tasks as in our study, found no effect of stress on the preparation effect and no effect on the RT switch cost; stress only led to a significant but small increase in the accuracy switch cost (stress group: 2.9%, control group: 1.4%; Plessow, Kiesel, & Kirschbaum, 2012). Both studies used a stress induction procedure that involved a psychological component (social evaluation and increased cognitive load), but not a physiological component such as our cold pressor test. Plessow and colleagues confirmed the success of their stress manipulation by examining salivary cortisol levels; Steinhauser and colleagues report no cortisol data. Neither study controlled for cue-repetition effects, and therefore both studies examined a confounded measure of task-switching ability. More research is needed to fully understand the effect of acute stress on task switching.

We found no effects of tVNS (versus sham) and tVNS intensity on measures of task switching (Figures 4 and 5). A previous study found that invasive VNS (vs. sham) impaired cognitive flexibility of patients with epilepsy on an anagram task (Ghacibeh et al., 2006), so more research is needed in this area. In a post hoc exploratory analysis, we found that tVNS at a higher intensity was associated with a speed–accuracy tradeoff: Stimulation at 1.0 mA resulted in faster (Δ 35 msec) but less accurate responses (Δ 1.0%; Figure 4). This finding seems at odds with findings that invasive VNS decreases excitability of the motor cortex in active rats (Mollet et al., 2013), even at mild stimulation

intensities, which would predict slower and more accurate responses. One study examined effects of tVNS on excitability of the motor cortex in healthy human volunteers (Capone et al., 2015). However, this study was underpowered ($n = 10$), used an unusually high stimulation intensity (8.0 mA), and did not find significant effects after correction for multiple statistical comparisons. Thus, our finding that 1.0 mA changes the speed–accuracy tradeoff requires replication, preferably augmented with measurements of motor cortex excitability.

Finally, although we used a drug (atomoxetine) and dose (40 mg) known to influence various aspects of cognitive task performance and cortical state (Pfeffer et al., 2018; van den Brink, Nieuwenhuis, & Donner, 2018; Warren, Wilson, et al., 2017; Jepma et al., 2016), even our pharmacological manipulation failed to modulate task-switching performance (Figures 6 and 7). Two other pharmacological studies have yielded consistent results. One study found no effect of the beta-adrenergic antagonist propranolol (80 mg) on switch costs (Steenbergen et al., 2015). However, there is some evidence that higher-order cognitive flexibility is mediated by alpha receptors, not beta receptors (Lapiz & Morilak, 2006). Another study found no effect on switch costs of the dopamine and NE transporter blocker methylphenidate (20 mg; Froböse et al., 2018). Neither study was designed to examine the preparation effect.

Although the cortical areas involved in task switching are rather well known (Worringer et al., 2019), very little is known about the neurochemical basis supporting efficient task switching. In a much-cited review, Kehagia et al. (2010) hypothesized that task switching may have a noradrenergic substrate, similar to extradimensional set shifting, another example of higher-order cognitive flexibility. Although the present findings suggest that, in healthy young adults, NE does not play an important role in task switching, this does not rule out the possibility that excessive flexibility/rigidity in patients with attention-deficit hyperactivity disorder, Parkinson disease, and other disorders is caused in part by noradrenergic dysfunction and can be treated with medication acting on the noradrenergic system.

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