*Neuroscience* 295 (2015) 237–242

# NO ROLE OF BETA RECEPTORS IN COGNITIVE FLEXIBILITY: EVIDENCE FROM A TASK-SWITCHING PARADIGM IN A RANDOMIZED CONTROLLED TRIAL

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**Abstract—There is evidence that noradrenergic coeruleo-cortical projections are involved in different forms of cognitive flexibility. So far, no studies in humans have investigated the involvement of beta receptors on task-switching performance, a well-established measure of cognitive flexibility. The present study investigated whether the administration of propranolol (a central and peripheral beta-adrenergic antagonist) affected switching costs (i.e., the increase of reaction time in task-switching trials relative to task-repetition trials). Sixteen healthy adult human subjects performed a global–local task-switching paradigm in a double-blind, within-subjects design study investigating the effects of 80 mg of propranolol hydrochloride (a β1 and β2 adrenergic receptor antagonist) vs. an oral dose of microcrystalline cellulose (placebo pill). The acute administration of propranolol did not affect the size of switching costs compared to the intake of the neutral placebo. Our results, corroborated by Bayesian inference, suggest that beta receptors do not modulate cognitive flexibility as measured by task-switching performance.** 

**Key words: norepinephrine, beta receptors, cognitive flexibility, task-switching.**

## INTRODUCTION

The animal literature suggests that various forms of cognitive flexibility, such as shifting attention between perceptual dimensions, are mediated by the activity of the locus coeruleus (LC)–norepinephrine (NE) system (see Robbins and Arnsten, 2009, for a review). In rats, augmenting noradrenergic activity at α-1-receptors in the medial prefrontal cortex promotes cognitive performance in an attentional set-shifting task (Lapiz and Morilak, 2006). Comparable improvements in set shifting have been achieved by chronic treatment with desipramine, an NE-reuptake blocker, and atipamezole, an α-2-adrenergic autoreceptor antagonist (Lapiz et al., 2007; Bondi et al., 2010). Moreover, lesions of the dorsal noradrenergic bundle created by 6-hydroxydopamine, which causes substantial depletions of cortical NE, seem to selectively impair set shifting (Tait et al., 2007). Last, specific decrements in attentional set-shifting task were obtained in rats after noradrenergic but not cholinergic deafferentiation (McGaughy et al., 2008). In humans, NE reuptake inhibitors, such as atomoxetine, have been suggested as potential cognitive enhancers in schizophrenia because of their capacity to indirectly but selectively increase extracellular dopamine concentrations in the prefrontal cortex (Friedman et al., 2004). Moreover, propranolol (a central and peripheral β-adrenergic antagonist) and nadolol (peripheral β-adrenergic antagonist) have been found to modulate mean time-to-solution in insight problem-solving, a function related to cognitive flexibility (Beversdorf et al., 1999, 2002; Campbell et al., 2008).

The goal of the present study was to examine in humans whether cognitive flexibility can be modulated by NE using task switching performance, a reliable indicator of cognitive flexibility (Miyake et al., 2000; Monsell, 2003). The total time to switch between two different tasks (i.e., switching costs) can be taken to reflect the efficiency of adapting and restructuring cognitive representations, so that smaller switching costs indicate a higher degree of cognitive flexibility. In this type of paradigm, the sequence of tasks is often predictable and consistent (e.g., AABBAABB. . .). Therefore, participants know when to prepare for a task switch, so that the interval between the previous response and the upcoming stimulus (the response–stimulus interval or RSI) can be considered a preparation interval. In switch trials, participants can use this preparation interval to reconfigure their cognitive task set.

Given that propranolol has been found to modulate insight problem-solving (Beversdorf et al., 1999, 2002; Campbell et al., 2008), a function related to cognitive flexibility, in the present study we investigated whether the administration of propranolol affects the size of switching costs. Based on the evidence suggesting a pivotal role of NE in driving cognitive flexibility (Robbins and Arnsten, 2009), we predicted larger switching costs after propranolol intake than after the intake of a neutral placebo.

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*Abbreviations:* $H_0$, null hypothesis; LC, locus coeruleus; ms, miliseconds; NE, norepinephrine.

http://dx.doi.org/10.1016/j.neuroscience.2015.03.049
0306-4522/

## EXPERIMENTAL PROCEDURES

### Participants

Sixteen healthy native Dutch-speaking subjects [eight male, mean age (SD) = 24.3 (3.5); eight female, mean age = 22.6 (3.4)] took part in our studies in return for 100 Euros. Only participants with a systolic blood pressure above 100 mmHg, a diastolic blood pressure above 60 mmHg and a resting heart rate above 60 beats per minute were included in the study. All volunteers gave written informed consent. Participants were screened to be free of neurological, psychiatric and physical illness and had not been on any medication for at least 3 months. All subjects were medically screened and considered to be in satisfactory health. Subjects received an oral dose of 80 mg of propranolol hydrochloride (a β1 and β2 adrenergic receptor antagonist) or 80 mg of cellulose microcrystalline (placebo pill) in a double-blind, randomized and counterbalanced, within-subjects design. Propranolol and placebo were administered to each participant on consecutive days (24 h in between administrations). Drug allocation was balanced for gender. Heart rate, and systolic and diastolic blood pressure were measured immediately before drug administration (time 0 min) and at the beginning (time + 205 min) and end of the task-switching paradigm (time + 230 min). One subject was excluded from the study because of the severe side effects (cardiorespiratory arrest) after propranolol ingestion (de Rover et al., 2010, see also de Rover et al., 2012). Data of one other additional participant were omitted, as he committed more than 30% of errors performing the task-switching paradigm. The study was approved by the medical ethics committee of the Leiden University Medical Center and was conducted according to the Declaration of Helsinki.

### Procedure

Each subject was tested at approximately the same time of the day (noon). Subjects were instructed to abstain from alcohol, but also caffeine, nicotine, and other psycho-active substances from 15 h before the start of the session until the day after the session. After the medical screening, participants received a microcrystalline cellulose-filled capsule with either propranolol or placebo ($t = 0$). Immediately after that participants performed a passive viewing task (results reported in de Rover et al., 2010 - experiment 2), an auditory oddball task and a flanker task (Unpublished results). The task-switching paradigm (described in details below) was performed between $t = 205$ and $t = 230$ min post treatment. After completion of the tasks, the subjects were debriefed and paid. At $t = 240$, subjects were reevaluated and sent home when blood pressure was (near) normal.

### Task-switching paradigm

The experiment was controlled by a Windows-operated computer attached to a Philips 17″ monitor. Responses were made by pressing the "Z" or "/" of the QWERTY computer keyboard with the left and right index fingers, respectively. The target stimuli were adopted from Colzato et al. (2010) and Christoffels et al. (2014) and consisted of geometric figures. Larger (global) rectangles/squares consisted of smaller (local) rectangles or squares. Global stimuli (i.e., squares or rectangles; 93 × 93 pixels or 41 × 189 pixels respectively) were composed of many smaller "local" stimuli (i.e., squares or rectangles; 21 × 21 pixels or 8 × 46 pixels respectively). The space between the local elements of a stimulus was 3 pixels. A global square consisted of 16 small squares or 16 small rectangles; a global rectangle consisted of 16 small squares or 16 small rectangles. The "local" and "global" cues were the same size as the global and local stimuli and were presented at 189 pixels from the center of the computer screen.

Participants were presented with one of the four possible stimuli: a rectangle consisting of smaller rectangles or squares, or a square consisting of smaller rectangles or squares. A cue (a rectangle and square, congruous in location with the associated response button) appeared 400–600 miliseconds (ms) before the stimulus (located at the center of the screen, between the two cues). The cue was either small or large, and indicated to which level (global/local) the participants should attend in the upcoming stimulus (see Fig. 1). The rectangle or square was associated with a spatially assigned response button that was pressed with either the left ("Z" from a QWERTY keyboard) or right ("/" from a QWERTY keyboard) index finger. Which stimulus corresponded to which button was counterbalanced across participants. The four possible stimuli made that trials could either be congruent or incongruent. A congruent trial was a bigger shape built up out of similar smaller shapes (e.g., a large square consisting of smaller squares), an incongruent trial a bigger shape built up out of different smaller shapes (e.g., a large square consisting of smaller rectangles). Both the color of cues and the color of the target stimulus were red, and both remained on the screen until a response was given or 2500 ms had passed. The interval between response and presentation of the next cue was 900–1100 ms (See Fig. 1). In total, three blocks of trials were administered. The first two blocks consisted of 50 trials each, and were training blocks in which the dimension to be attended (global or local) was constant across all trials within that block. Training block order was counterbalanced between participants, meaning that half of the participants started with the "local block", the other half with the "global block". In the third, experimental block of 160 trials, participants had to switch between attending to the global or local dimension every four trials. Using this task, trials could simultaneously be, for example, global, incongruent, and repetition trials. Because of this, participants performed on a total of 80 congruent trials, 80 incongruent trials, 80 global trials and 80 local trials, 39 switch trials, and 120 repetition trials (excluding the very first trial, as it is not a repetition, nor a switch trial).

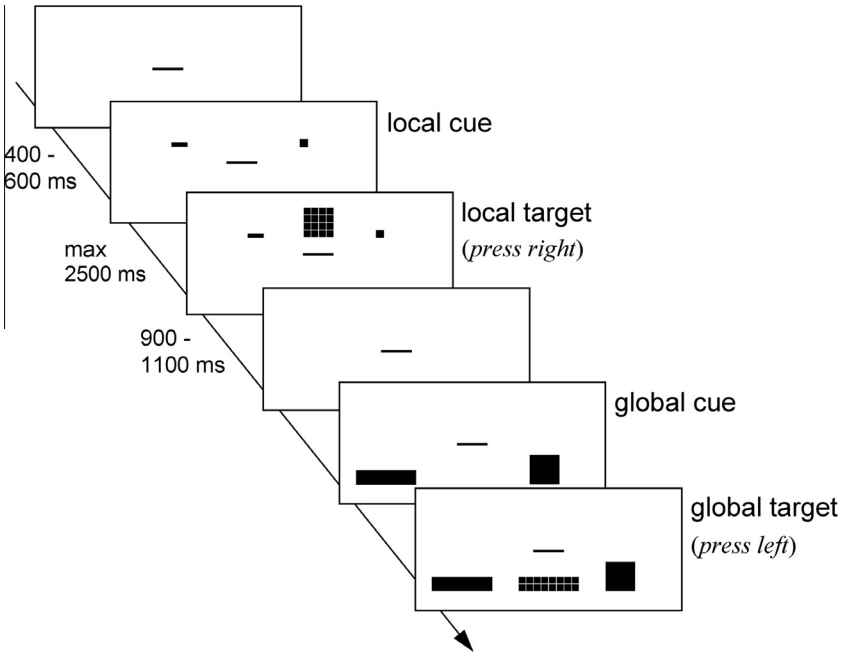


**Fig. 1.** Sequence of events in the experimental block; where participants had to switch between responding to the local level and the global level.

### Statistical analysis

Heart rate was analyzed separately by means of repeated-measures analyses of variance (ANOVAs) with treatment (propranolol vs. placebo) and effect of time (first vs. second vs. third measurement) as within-subjects factor.

Mean RTs and proportions of errors were analyzed by means of ANOVAs using treatment (propranolol vs. placebo), target level (global vs. local), the congruency between the stimuli on the two levels (congruent vs. incongruent), and task switch (i.e., same vs. different target level as in previous trial: task repetition vs. alternation) as within-subjects factor. A significance level of $p < .05$ was adopted for all tests.

## RESULTS

### Cardiovascular measurements

Table 1 presents the absolute values of heart rate (in beats per minute), as observed before drug administration, at the beginning, and the end of the experimental session, for both treatments (propranolol vs. placebo). Heart rate showed a significant effect of time, $F(2,28) = 105.82$, $p < 0.001$, $\eta_p^2 = 0.88$. Time and treatment were involved in a significant interaction, $F(2, 28) = 10.53$, $p < 0.001$, $\eta_p^2 = 0.43$, indicating that heart rate decreased significantly more over time after the intake of propranolol as compared to placebo. Tukey HSD post hoc tests showed that the baseline heart rate did not differ between propranolol and placebo treatment ($p = 0.34$), whereas the heart rate was significantly lower after the intake of propranolol as compared to placebo at pre-test ($p < 0.005$) and at post-test measurements ($p < 0.05$).

**Table 1.** Means of cardiovascular measurement (heart rate) for placebo and propranolol intake are shown at BL = Baseline; Pre-test = 205 min after baseline, right before the start of the task-switching paradigm; Post-test = right after the end of the task. Standard errors are shown within parentheses

| Treatment | Placebo | Propranolol |
|---|---|---|
| Heart rate | | |
| BL | 74.3 (2.6) | 77.5 (3.8) |
| Pre-test* | 58.3 (2.2) | 51.3 (2.4) |
| Post-test* | 54.8 (2.7) | 53.2 (2.2) |

* $p < 0.05$ (significant group difference).

### Task-switching paradigm

The reaction time analysis showed only two significant sources of variance (see Table 2). First, the effect of switching, $F(1,13) = 47.04$, $p < .0001$, MSE = 2228.21, $\eta_p^2 = 0.78$, which revealed that repeating the task allowed for faster responding than switching between target levels (374 vs. 418 ms). Second, the effect of target level, $F(1,13) = 92.27$, $p < .0001$, MSE = 1552.07, $\eta_p^2 = 0.87$, reflecting the well-known global precedence (Navon, 1977), that is, faster responses to globally than locally defined targets (371 vs. 421 ms). Crucially, the size of the switch effect did not vary with treatment, $F < 1$ (see Fig. 2) – a finding at odds with the hypothesis that cognitive flexibility may be mediated by the activity of the LC–NE system. Given that conventional null-hypothesis significance testing (NHST) cannot be used to provide evidence in favor of the null hypothesis ($H_0$), we applied a Bayesian approach to evaluate the robustness of this outcome. Specifically, we calculated the Bayesian information criterion (BIC) to estimate the Bayes factor and generate the posterior probability associated with the occurrence of $H_0$, given the observed data, i.e., $p(H_0|D)$ (see Masson,

**Table 2.** Mean reaction times (RT; in ms) and errors (in %) for each condition in the global–local task-switching paradigm as a function of placebo and propranolol treatment are displayed. Standard errors are shown in parentheses

| Treatment | Placebo | | Propranolol | |
|---|---|---|---|---|
| | Mean RT | Mean error | Mean RT | Mean error |
| Switch | 425 (22.2) | 6.7 (1.3) | 410 (12.4) | 4.7 (0.9) |
| Repetition | 379 (13.5) | 6.6 (1.1) | 370 (9.1) | 6.5 (0.9) |
| *Switch cost* | *47 ms* | | *40 ms* | |
| Local target | 429 (19.5) | 8.3 (1.2) | 413 (11.7) | 6.1 (0.9) |
| Global target | 375 (16.4) | 5.0 (1.2) | 366 (10.1) | 5.1 (0.9) |
| *Global precedence* | *54 ms* | | *47 ms* | |
| Incongruent | 409 (16.8) | 10.9 (1.6) | 395 (12.1) | 8.4 (1.2) |
| Congruent | 395 (19.9) | 2.4 (0.5) | 385 (9.6) | 2.7 (0.7) |
| *Congruency effect* | *13 ms* | | *10 ms* | |

2011, and Wagenmakers, 2007 for further details about the procedure). The $p(H_0|D)$ provides the exact probability of the occurrence of $H_0$. The analysis revealed that the $p(H_0|D)$ was 0.76, hence, on the basis of the guidelines proposed by Raftery (1995), represents positive evidence in favor of $H_0$.

The analysis of the error rates revealed two reliable main effects. First, the effect of congruency, $F(1,13) = 37.67$, $p < .0001$, MSE = 75.69, $\eta_p^2 = 0.74$, reflecting interference of the irrelevant target level, as indicated by a smaller proportion of errors on congruent as compared to incongruent trials (2.5% vs. 9.7%). Second, the effect of target level, $F(1,13) = 6.00$, $p < .05$, MSE = 43.49, $\eta_p^2 = 0.32$, suggesting less errors in globally than in locally defined targets (5.0% vs. 7.2%). Target level and congruency significantly interacted, $F(1,13) = 11.09$, $p < .01$, MSE = 21.56, $\eta_p^2 = 0.46$, showing that the congruency effect was larger in the local task (9.2 %) compared to the global task (5.1%). Congruency was involved in a three-way interaction with switch and treatment, $F(1,13) = 6.58$, $p < .05$, MSE = 26.18, $\eta_p^2 = 0.34$. Tukey HSD post hoc tests showed that, when the task alternated, the congruency effect was larger after placebo (11.39%) compared to propranolol intake (5.11%), $p < .05$, whereas when the task repeated, the congruency effect after placebo intake (5.65%) was comparable to propranolol intake (6.39%), $p = 0.98$.

## DISCUSSION

Our results, corroborated by Bayesian inference, suggest that beta receptors do not directly influence the size of switching costs, a well-established measure of cognitive flexibility. Given the evidence, coming mainly from the animal literature, suggesting that different forms of cognitive flexibility are mediated by the activity of the LC-NE system (Lapiz and Morilak, 2006; Lapiz et al., 2007; Tait et al., 2007; Bondi et al., 2010), we expected

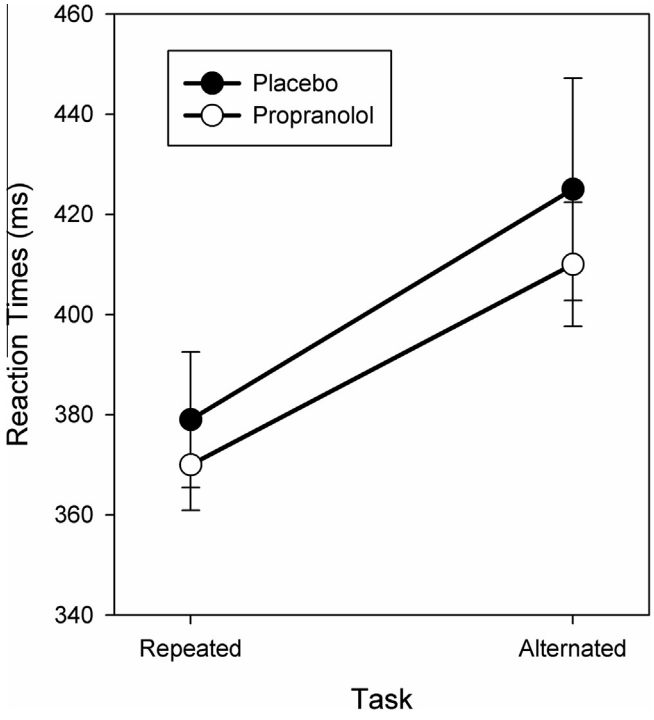


**Fig. 2.** Mean reaction times (in miliseconds, ms) as a function of treatment (propranolol vs. placebo) and task switch (i.e., same vs. different target level as in previous trial: task repetition vs. alternation). Error bars represent standard errors.

the acute administration of propranolol, a β1 and β2 adrenergic receptor antagonist, to cause a detectable impairment in cognitive flexibility. The non-significant effect on switching costs we observed casts some doubts on the assumed critical role of NE in mediating cognitive flexibility in humans (Robbins and Arnsten, 2009), at least as indexed by task-switching efficiency. The only reliable effect involving treatment was the congruency effect in the error rates: The effect of congruency, which reflects a failure to suppress the currently irrelevant task in working memory (see for a review, Kiesel et al., 2010), was reduced after propranolol intake when the task alternated. This observation fits with the finding of Oei et al. (2010), that the same dose of 80 mg propranolol reduces distraction in working memory.

We can only speculate what the reasons for this outcome pattern are. First, it may be that our task, experimental design and sample size were not sufficiently sensitive to reveal within-subject differences. However, a previous study using a within-subject design, roughly similar group sizes and the same subject population, had no difficulty in detecting within-levels effects on task-switching performance after the acute administration of tyrosine (Steenbergen et al., 2015).

Second, in our study we used an oral dose of 80 mg propranolol. On the one hand, our observation that heart rate was reduced in the experimental session suggests that our manipulation of blocking beta receptors worked as expected. On the other hand, however, NE is assumed to relate to cognitive performance in an inverted U-shaped function, which raises the possibility that a lower drug dose might have yielded stronger effects. However, the same dose was sufficient to reduce distraction in working memory in Oei et al. (2010), which renders this possibility not particularly likely.

Third, propranolol, our drug of choice, is a β1 and β2 adrenergic receptor antagonist. It remains to be investigated whether the current findings generalize to other noradrenergic drugs acting on α2 adrenoceptors, such as clonidine, or the selective NE transporter inhibitor atomoxetine. However, atomoxetine has been shown to increase both NE and dopamine in the prefrontal cortex (Bymaster et al., 2002). Further, follow-up studies might consider a more thorough exploration using multiple doses, a larger sample size and, by having a larger task battery, include different forms of cognitive flexibility.

A limitation of the study is that propranolol is not only an unselective beta-adrenergic receptor blocker but acts as a potent antagonist at 5-HT1A and 1B receptors as well (Oksenberg and Peroutka, 1988). 5-HT1A and beta-adrenergic receptors are both guanine nucleotide-binding protein-coupled receptors with a similar transmembrane topology and both receptor types show a strong overlap in their amino acid sequences. Thus, certain beta-adrenergic receptor antagonists, such as pindolol or propranolol, also bind to the 5-HT1A receptor with relatively high affinity (Guan et al., 1992). Consequently, the 5-HT1A receptor antagonism of propranolol might have masked behavioral effects potentially induced at beta-adrenergic receptors.

Taken altogether, there is rapidly growing interest in the specific role of the LC–NE system in cognitive flexibility (Robbins and Arnsten, 2009). In the future, psychopharmacological data from humans will be of critical importance in testing and further developing hypotheses that are based on neurophysiological observations in animals.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

*Acknowledgments—The study was funded by NWO (Netherlands Organization for Scientific Research) VIDI grant awarded to Sander Nieuwenhuis.*

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*(Accepted 20 March 2015)*
*(Available online 27 March 2015)*