The role of the locus coeruleus-noradrenaline system in temporal attention and uncertainty processing

Brown, S.B.R.E.

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Author: Brown, Stephen B.R.E.
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# 3. Effects of clonidine and scopolamine on multiple target detection in rapid serial visual presentation

Abstract

In this study we examined the effects of clonidine and scopolamine on multiple-target detection in a rapid serial visual presentation task to assess the role of the central noradrenergic and cholinergic systems in temporal attention. Eighteen healthy volunteers took part in a crossover double-dummy study in which they received clonidine (150/175 µg), scopolamine (1.2 mg) and placebo by mouth in counterbalanced order. A dual-target attentional blink task was administered at 120 min after scopolamine intake and 180 min after clonidine intake. The electroencephalogram was measured during task performance. Clonidine and scopolamine both impaired detection of the first target (T1). For clonidine, this impairment was accompanied by decreased amplitudes of the P2 and P3 components of the event-related potential. The drugs did not impair second-target (T2) detection, except if T2 was presented immediately after T1. The attentional blink for T2 was not affected. These and other results suggest that clonidine and scopolamine may impair temporal attention through a decrease in tonic alertness, and that this decrease in alertness can be temporarily compensated by a phasic alerting response to a salient stimulus. The comparable behavioral effects of clonidine and scopolamine are consistent with animal studies indicating close interactions between the noradrenergic and cholinergic neuromodulator systems.

This chapter is based on:

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3.1 Introduction
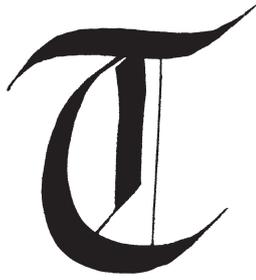
T̲emporal attention—the dynamic changes in attention on a fast timescale—is widely studied because it is crucial for organisms to be able to prioritize and accurately identify incoming information, for example to make successful decisions. In recent years, the neuromodulatory basis of temporal attention has attracted considerable scientific interest. One theory relates temporal attention to the noradrenergic neuromodulator system. This theory is founded on the idea that the release of noradrenaline by the locus coeruleus (LC) adjusts the gain of postsynaptic neurons, thereby modulating these neurons' responsivity (Servan-Schreiber, Printz, & Cohen, 1990). The LC has been demonstrated to fire phasically following the presentation of task-relevant or salient stimuli (Aston-Jones, Rajkowski, & Cohen, 2000) and these phasic bursts are temporally closely related to behavioral responses (Bouret & Sara, 2004). These findings suggest that the phasic LC response acts as a temporal attention filter that selectively facilitates the processing of motivationally significantly stimuli (Aston-Jones & Cohen, 2005; Nieuwenhuis, Aston-Jones, & Cohen, 2005a).

Rapid changes in temporal attention are commonly studied with the attentional blink task, in which participants have to identify two targets that are embedded in a rapid serial visual stream (RSVP) of distractor stimuli. Participants are usually able to accurately identify the first of those targets (T1). The crucial finding in this task is that when the second target (T2) follows the first target within 200-400 ms, participants are often unable to report T2 accurately (Raymond, Shapiro, & Arnell, 1992; Chun & Potter, 1995). This phenomenon is referred to as the attentional blink.

Nieuwenhuis and colleagues have proposed a theory in which the attentional blink reflects the temporal dynamics of the noradrenergic system

(Nieuwenhuis, Gilzenrat, Holmes, & Cohen, 2005b; see also Warren et al., 2009). This theory assumes that identification of T1 is associated with a transient burst of arousal and concomitant phasic firing of the LC. Following this T1-related phasic burst, LC neurons enter a refractory period of reduced firing. During this period, no noradrenaline-mediated facilitation of stimulus processing can occur. The characteristic attentional blink window of 200-400 ms corresponds to the duration of this refractory period, which would explain why participants often fail to detect T2 if it is presented within this time window. This theory also accounts for the phenomenon of lag-1 sparing (Raymond et al., 1992; Hommel & Akyürek, 2005): participants generally do detect T2 if it directly follows T1 (i.e. at "lag 1"). When there is such a close temporal proximity of T1 and T2, detection of T2 is proposed to benefit from the phasic noradrenaline burst elicited by T1 (Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999).

There is direct empirical evidence for the involvement of the noradrenergic system in target detection under rapid serial visual presentation conditions. For example, antagonization of noradrenergic β-receptors by propranolol led to impaired T2 identification in humans (de Martino, Strange, & Dolan, 2008). Furthermore, patients with dopamine-β-hydroxylase deficiency, a rare genetic syndrome characterized by the complete absence of noradrenaline, were shown to have a larger attentional blink than healthy controls, and this impairment was restored by treatment with a synthetic precursor of noradrenaline (Jepma, et al., 2011). However, when Nieuwenhuis, van Nieuwpoort, Veltman, and Drent (2007) used the noradrenergic α_2 agonist clonidine to attenuate noradrenergic baseline activity, they did not find a reliable decrease in T2 identification accuracy, a finding that seems at odds with the theory of Nieuwenhuis et al. (2005b).

The goal of the present experiment was to replicate the study by Nieuwenhuis et al. (2007), but with two improvements: a crossover design instead of a between-subjects design to increase statistical power; and an increased dose of

clonidine to induce a more pronounced attenuation of the noradrenergic system. Furthermore, we recorded the electroencephalogram (EEG) to acquire more insight into the electrophysiological correlates of treatment effects on RSVP performance.

We tested 18 healthy adult participants in a double-blind placebo-controlled randomized crossover design. Participants received, in different test sessions, a single dose of clonidine, scopolamine and placebo. Clonidine is a centrally-acting α_2 agonist that attenuates baseline noradrenergic activity by agonizing pre-synaptic α_2 receptors, and decreases the amplitude of the human P3 component, a putative electrophysiological correlate of phasic noradrenaline release (Nieuwenhuis, Aston-Jones, & Cohen, 2005a; Pineda, Foote, & Neville, 1989). If the attentional blink is mediated by a phasic noradrenergic burst following presentation of T1, and clonidine decreases this phasic burst, then clonidine may be expected to reduce the attentional blink. Notably, previous event-related potential (ERP) studies have associated the attentional blink with a larger or a delayed T1-elicited P3 (Martens, Munneke, Smid, & Johnson, 2006; Sergent, Baillet, & DeHaene, 2005; Slagter et al., 2007). We were thus specifically interested in possible effects of clonidine on the T1-elicited P3.

The involvement of the cholinergic system in temporal attention has been investigated less extensively than that of noradrenaline. Previous empirical work has focused on the nicotinic cholinergic system and has not studied RSVP performance, but other temporal attention tasks like temporal cuing (e.g., Beane & Marrocco, 2004; Stewart, Burke & Marrocco, 2001). Therefore, we also administered the muscarinic antagonist scopolamine, a drug with a sedation profile comparable to that of clonidine. The use of scopolamine allowed us to gain insight into the role of the cholinergic muscarinic system in temporal attention and to test whether any treatment effects are specific to the noradrenergic system.

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3.2 Methods and Materials

3.2.1. Participants

Eighteen healthy young adults (15 women), aged 18-26 years (mean age 21 years), drafted through Leiden University's participant recruitment system, took part in three 4.5-hour experimental sessions in return for €140. Only participants with a systolic blood pressure above 100 mmHg, a diastolic blood pressure above 70 mmHg and a heart frequency over 65 beats per minute in rest were included in the study (cf. Nieuwenhuis et al., 2007). All participants underwent a medical screening which included a routine physical examination prior to being included in the experiment: only healthy individuals without a history of neurological or psychiatric disorders were allowed to participate. Participants took no prescribed medication and did not smoke; participants were instructed to abstain from using recreational drugs, caffeine, or alcohol 15 hours prior to the study. Participants received a single oral dose of clonidine, a single oral dose of scopolamine (1.2 mg), and a placebo in a randomized, double-blind, counterbalanced double-dummy crossover design. The first 11 participants received a clonidine dose of 175 µg. As the eleventh participant showed an unexpected large drop in blood pressure of 35 mmHg systolic, but without clinical consequences, 60 minutes after the ingestion of clonidine 175 µg (blind was broken by the supervising physician), we decided to reduce the dose of clonidine to 150 µg for the final 7 participants. Preliminary repeated-measures ANOVAs with dose as between-subject factor revealed no reliable main effect of dose or interactions including this factor, so in the analyses reported below the 18 participants are pooled. Clonidine, scopolamine, and placebo were administered during three separate test sessions, spaced one week apart. The study was approved by the medical ethics committee of the Leiden University Medical Center. Written informed consent was obtained from all participants prior to inclusion in the study.

3.2.2. Task

Participants performed an attentional blink task. Each trial started with a 500-ms fixation point (black plus-sign on light grey background, visual angle 0.6 x 0.6°), followed by a 2-s blank, after which a RSVP stream of 22 uppercase letters was presented centrally (visual angle of each letter approximately 0.7 x 0.7°). Each letter was randomly drawn without replacement from the alphabet and presented for 74 ms, followed by a blank of 24 ms. The letters *I*, *O*, *Q*, and *S* were left out, as they resemble digits too much. On each trial, two letters were replaced by digits (range 2-9, chosen randomly without replacement): targets 1 and 2 (T1 and T2). T2 was presented three to six temporal positions from the end of the stream. The temporal distance between T1 and T2 was either one (12.5% of trials), two (37.5% of trials), three (37.5% of trials), or seven items (12.5% of trials), corresponding to lags of 98, 196, 294, and 658 ms. Immediately after the end of the RSVP stream, participants were asked to identify T1 and T2 by typing them, in order, on a standard keyboard. The task consisted of 6 blocks of 40 trials each, and was preceded by a practice block of 12 trials, in which feedback on the participants' performance was given on every trial (e.g., a display of "+ −" indicated that a participant had entered T1 correctly and T2 incorrectly).

3.2.3. Procedure

Each participant was tested at approximately the same time of day. During every test session participants received a capsule of clonidine or placebo at 09.35 AM and a capsule of scopolamine or placebo at 10.35 AM. The different kinetic profiles of clonidine and scopolamine necessitated administrations at different times prior to testing. This double-dummy design resulted in one clonidine session (i.e. clonidine verum plus scopolamine placebo), one scopolamine session (clonidine placebo plus scopolamine verum), and one placebo session (clonidine plus scopolamine placebos). To eliminate any possible confound of drug order, we

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stratified this factor by distributing the six possible drug orders evenly across participants.

At the start of each session (t = –20 min), a peripheral intravenous cannula was placed and connected to an intravenous 0.9% NaCl (saline) drip to be able to increase blood pressure through volume expansion and to have an entryway to administer escape medication in the case of a severe drop in tension and/or heart frequency. Furthermore, three cardio electrodes were applied to the participant's chest and connected to an electrocardiography (ECG) monitor. To measure the sedative, alertness-reducing properties of clonidine and scopolamine, we administered a 40-trial simple reaction time task (SRT) task upon a participant's arrival in the lab, as well as right before and after the participant performed the attentional blink task. Participants had to respond as quickly as possible whenever a white circle appeared on the computer screen. Stimulus onset asynchrony was jittered between 500-1250 ms, with a mean of 1000 ms; this task lasted less than two minutes.

At t = 0 min, participants ingested a microcrystalline cellulose-filled capsule with either clonidine or placebo. Clonidine has well-established antihypertensive properties: therefore, blood pressure and heart rate were monitored four times an hour from t = 0 onwards for participant safety with an Omron M10-IT automatic sphygmomanometer. At t = 60 min, participants ingested a microcrystalline cellulose-filled capsule with either scopolamine or placebo.

At t = 180, participants performed the attentional blink task which lasted approximately 30 minutes; during the 90 minutes prior to this time point, participants performed three unrelated cognitive tasks (Brown et al., 2015; Brown, van der Wee, van Noorden, Giltay, & Nieuwenhuis, submitted). Participant fitness was checked at t = 240, and participants were sent home via public transportation if their blood pressure and heart rate were close to the values measured at t = –20. At the end of the third test session, participants received their financial compensation.

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3.2.4. EEG recording and analyses

We recorded EEG from 64 Ag/AgCl scalp electrodes and from the left and right mastoids. We measured the horizontal and vertical electro-oculogram (EOG) using bipolar recordings from electrodes placed approximately 1 cm lateral of the outer canthi of the two eyes and from electrodes placed approximately 1 cm above and below the participant's right eye. The EEG signal was pre-amplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of 16x by a BioSemi ActiveTwo system (BioSemi B.V., Amsterdam). The data were digitized at 24-bit resolution with a sampling rate of 512 Hz using a low-pass fifth-order sinc filter with a half-power cutoff of 102.4 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode producing a monopolar (non-differential) channel, and was referenced offline to the average of the left and right mastoids. Data were high-pass filtered at 0.1 Hz and low-pass filtered at 30 Hz. Ocular and eyeblink artifacts were corrected using the method of Gratton, Coles, and Donchin (1983). Epochs with other artifacts (a gradient greater than 30 µV, slow drifts [>300 µV/200 ms], and low activity [<0.50 µV/100 ms]) were discarded (placebo: 1.2%, clonidine: 1.3%, scopolamine: 2.5%). Data were epoched from -100 to 600 ms relative to the onset of T1 and then averaged. A baseline, computed as the average signal activity across the 100 ms prior to T1, was subtracted for each ERP.

As the active compounds only reliably influenced T1 accuracy (regardless of lag), and given previous studies linking the T1-evoked P3 to the attentional blink (e.g., Martens et al., 2006; Sergent et al., 2005; Slagter et al., 2007), we focused our electrophysiological analyses on T1-evoked potentials. We analyzed the ERP elicited by T1 with a sliding-window approach to examine the main effect of treatment on T1 processing and its interaction with T1 accuracy, focusing in particular on electrodes Cz, CPz and Pz, where the P3 was largest in amplitude. We

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collapsed T1-locked ERPs across lags, then split the ERPs for each treatment and each participant into 19.5-ms windows, starting at t = 0 (i.e. 0-19.5 ms, 19.6-39 ms, etc.), averaged the amplitudes in each window across participants, and then submitted these averages to a repeated-measures ANOVA with treatment as a within-subjects factor. We considered the difference between the three treatments significant if at least two neighboring windows were significant at $p < .05$. To examine the interaction between treatment and T1 accuracy, we took the same approach but distinguished between correct and incorrect T1 epochs. In this analysis, we only included participants who had 15 or more trials in each cell of the design, which led to the inclusion of 11 participants. The other 7 participants made too few T1 errors.

3.3 Results

3.3.1. Physiological and alertness data

Figure 3.1A shows that, as expected, clonidine lowered systolic (mean tension 101 mmHg) and diastolic (65 mmHg) blood pressure relative to placebo (mean tension 112/73 mmHg), also during performance of the attentional blink task (t = 180-210), ps < .0005. The difference in systolic and diastolic blood pressure between placebo and scopolamine was not significant. Figure 3.1B shows that scopolamine (61/min), as expected, lowered heart frequency relative to placebo (71/min) and clonidine (69/min), also during performance of the attentional blink task, ps < .004.

Data from the SRT task (Figure 3.1C), administered at baseline (arrival of participant), right before, and right after performing the attentional blink task, yielded a main effect of treatment, $F(2, 34) = 4.7$, $p < .03$, partial $\eta^2 = .22$. Treatment did not interact with time, $F(4, 68) = 3.2$, $p = .07$, partial $\eta^2 = .16$. Pairwise comparisons indicated that clonidine and scopolamine reliably slowed down SRT compared to placebo during both the pre-test ($t_{17} = 3.0$, $p = .009$ and $t_{17} = 2.3$, $p = .03$, respectively) and the post-test ($t_{17} = 4.2$, $p = .001$ and $t_{17} = 3.2$, $p =$

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.006, respectively). The differences between clonidine and scopolamine were not significant.

3.3.2. Behavioral data

Trials on which T1 and T2 were accurately identified but in the wrong order were treated as correct (cf. Nieuwenhuis et al., 2007). Greenhouse-Geisser corrections were applied whenever the assumption of sphericity was violated; in such cases, uncorrected degrees of freedom are reported.

Figure 3.2 (left panel) shows average T1 accuracy as a function of treatment and lag. The main effect of treatment was significant, $F(2, 34) = 4.4$, $p = .02$, partial $\eta^2 = .21$. Both clonidine (79.3%, $t_{17} = 2.5$, $p = .02$) and scopolamine (79.4%, $t_{17} = 2.4$, $p = .03$) decreased T1 identification accuracy relative to placebo (85.6%). T1 identification accuracy increased with lag, $F(3, 51) = 6.6$, $p = .001$, partial $\eta^2 = .28$. Treatment and lag did not interact, $F(6, 102) = 0.2$, $p = .96$. To determine if the two drugs also decreased T2 accuracy, we examined average T2 accuracy, non-contingent on T1 identification, as a function of treatment and lag (Figure 3.2, middle panel). Treatment did not reliably influence T2 identification accuracy, $F(2, 34) = 1.6$, $p = .21$, partial $\eta^2 = .09$. T2 identification performance showed the characteristic pattern of lag-1 sparing, a subsequent decrease of accuracy for lags 2 and 3 (i.e. the attentional blink), and a recovery of performance for lag 7, $F(3, 51) = 12.1$, $p < .0005$, partial $\eta^2 = .42$. Treatment and lag did not interact ($p = .051$). We found it remarkable that the treatment effects for lag 1 were of a similar magnitude as those on T1 accuracy.

Indeed, although there was no overall effect of treatment, analysis of individual lags yielded a reliable effect of treatment for lag 1, $F(2, 34) = 5.8$, $p = .007$, partial $\eta^2 = .25$, but not for the other three lags (all $ps > .44$). Pairwise comparisons for lag 1 revealed that accuracy in the clonidine (76.6%; $t_{17} = 3.1$, $p = $

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.007) and scopolamine (79.1%; t_{17} = 2.9, p = .009) conditions was lower than in the placebo condition (87.7%), indicating that the treatment effects for T1 extended into lag 1 but not further. There was no reliable difference in accuracy between the clonidine and scopolamine conditions (p = .51).
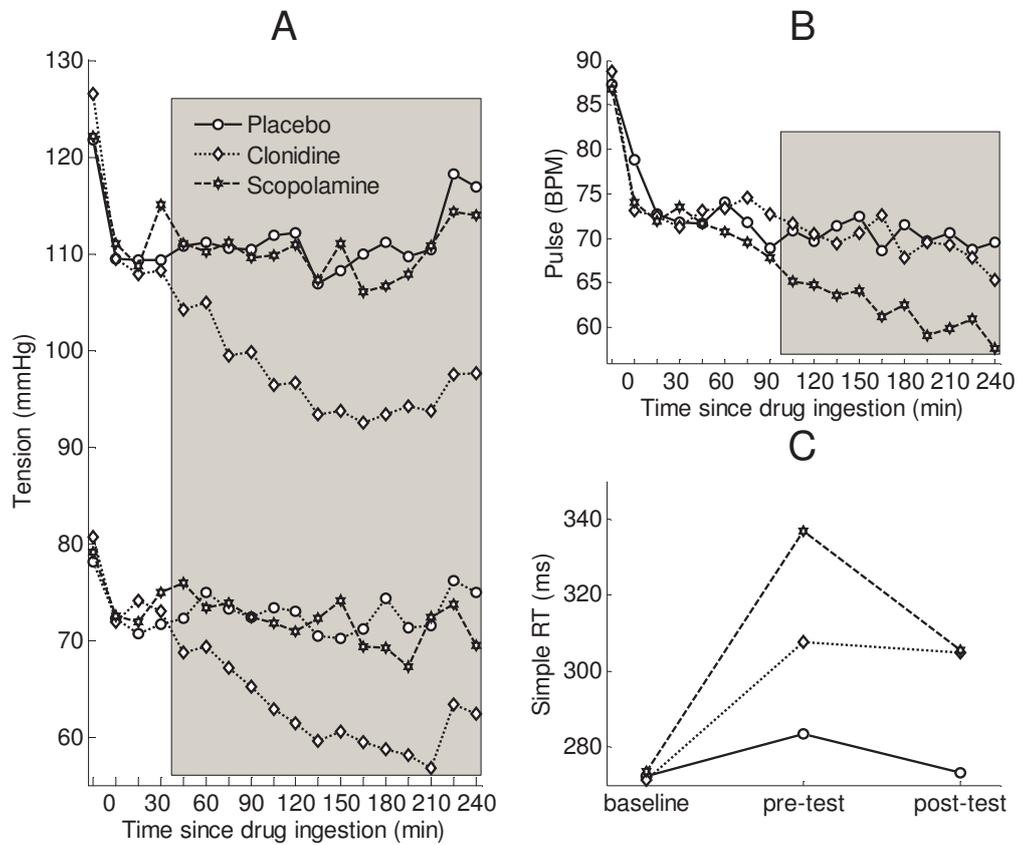

Figure 3.1A. Blood pressure data for the three treatments. The shaded grey area indicates significant pairwise comparisons between clonidine and placebo (p < .05). B. Heart frequency for the three treatments. The shaded grey area indicates significant pairwise comparisons between scopolamine and placebo (p < .05). C. Results from a simple reaction-time task, administered at the start of the test session (baseline) and right before (pre-test) and after (post-test) participants performed the attentional blink task.
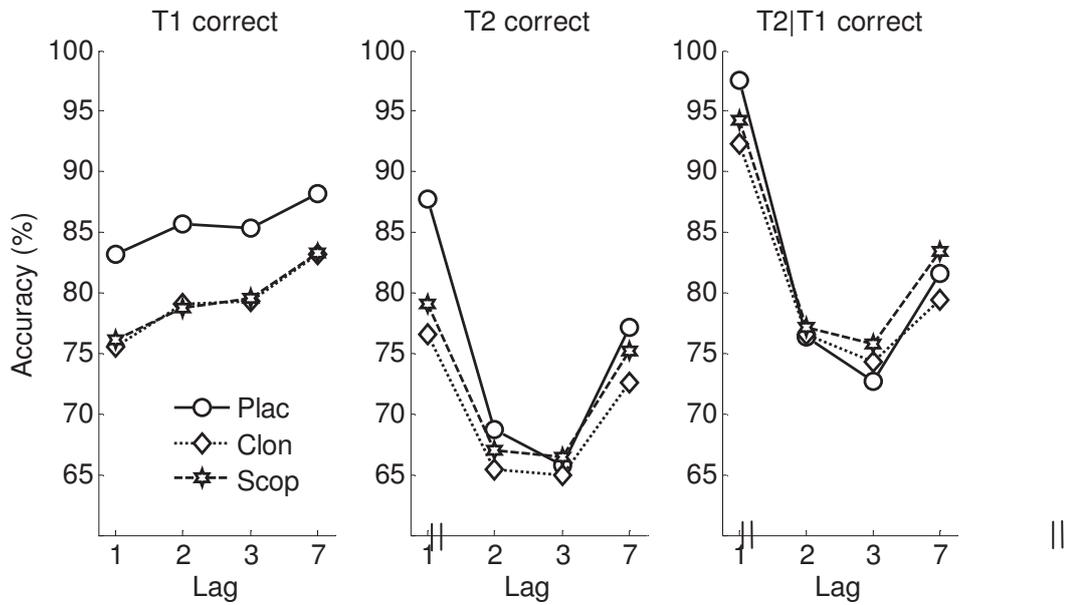
Figure 3.2. T1 identification accuracy (left panel), T2 identification accuracy (middle panel), and T2 identification accuracy (conditional upon T1 correct) as a function of treatment and lag.

Figure 3.2 (right panel) shows the results of a similar T2 analysis, but constrained to T1-correct trials, as is common in attentional blink research. This analysis yielded similar statistical results. Treatment did not reliably influence T2 identification accuracy, $F < 1$. There was a main effect of lag, $F(3, 51) = 18.6$, $p < .0005$, partial $\eta^2 = .52$, but no interaction between treatment and lag ($p = .33$). Again, separate analyses of the four lags yielded a reliable effect of treatment for lag 1 only, $F(2, 34) = 3.3$, $p = .05$, partial $\eta^2 = .16$. Pairwise comparisons for lag 1 revealed that T2 accuracy was lower in the clonidine (92.3%, $t_{17} = 2.3$, $p = .04$) and scopolamine ($t_{17} = 2.1$, $p = .05$) conditions than in the placebo condition (97.5%). There was no reliable difference in accuracy between the clonidine and scopolamine conditions ($p = .40$).

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3.3.3. Electrophysiological data

As the active components only reliably affected T1 accuracy, we next examined the effects of drugs on T1-evoked ERPs, including both correct and incorrect trials. As can be seen in Figure 3.3 (horizontal bars), the sliding-window approach led to the identification of two significant windows for electrode Cz: 197-236 ms (corresponding to the P2 component) and 373-412 ms (corresponding to the P3). The P2 effect was also significant for electrode CPz, suggesting a centroparietal locus of this effect. In the P2 window, clonidine was associated with a smaller mean amplitude (1.6 µV) than placebo (2.6 µV, t_{17} = 3.9, p = .001) and scopolamine (2.1 µV, t_{17} = 2.2, p = .046); the difference between placebo and scopolamine was not statistically significant (p = .19). In the P3 window, clonidine was also associated with a smaller mean amplitude (2.2 µV) than placebo (3.5 µV, t_{17} = 4.1, p = .001); scopolamine (3.0 µV) did not differ reliably from placebo (p = .30) and clonidine (p = .12). Thus, relative to placebo, clonidine attenuated the amplitude of the P2 and P3 components evoked by T1. Relative to scopolamine, clonidine attenuated the P2; the numerical difference in P3 amplitude was not significant.

Control analyses further clarified the nature of the treatment effects on P2 and P3 amplitude. First, the P2 and P3 effects were also clearly visible in T1-evoked ERPs that included only correct trials, suggesting that these treatment effects were not primarily driven by treatment effects on (number of included) incorrect trials. Second, examination of lag-specific T1-evoked ERPs indicated that the P2 and P3 effects were also present for longer lags, excluding the possibility that the effects constituted treatment effects on T2-related potentials that confounded the T1-evoked waveforms.
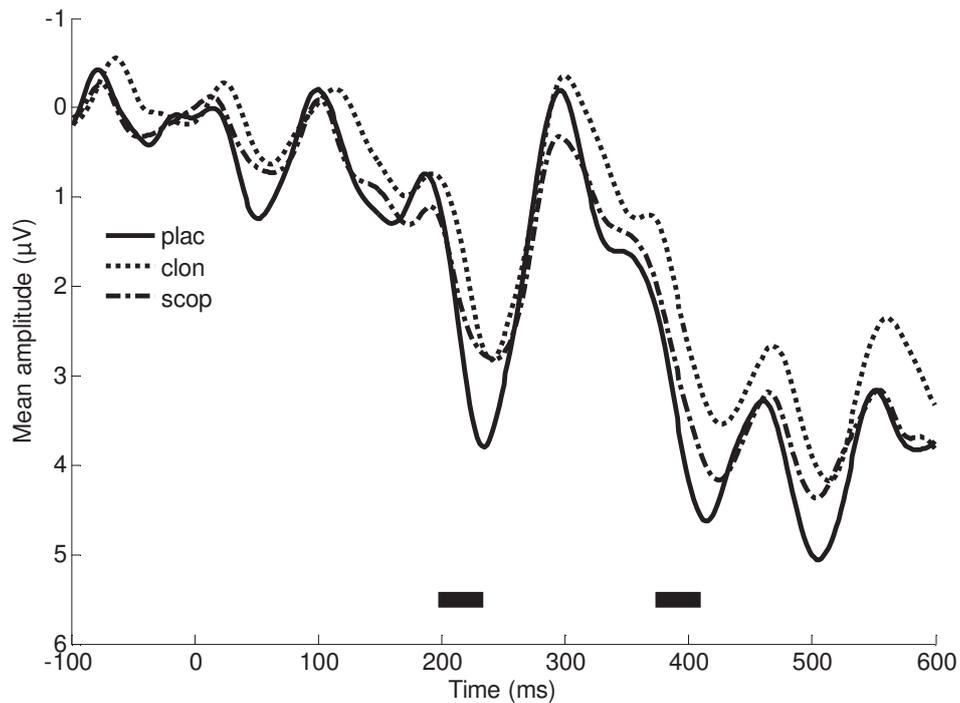
Figure 3.3. T1-locked grand average ERP waveforms for electrode Cz, plotted separately for each treatment. The horizontal black bars indicate windows where the main effect of treatment was significant (see Methods and Materials).

Perhaps due to the lower number of included participants and lower trial numbers in some conditions, and hence less precise estimates, a subsequent sliding-window analysis did not yield any windows with a significant interaction between treatment and T1 accuracy. Figure 3.4 shows mean amplitudes in the P2 and P3 windows identified in the previous analysis as a function of T1 accuracy and treatment. P3 amplitude is somewhat reduced on T1-incorrect trials, consistent with findings of reduced P3 amplitudes on T2-incorrect (i.e. attentional-blink) trials (e.g., Rolke, Heil, Streb, & Hennighausen, 2001; dell'Acqua, Jolicoeur, Pesciarelli, Job, & Palomba, 2003). Accordingly, the P3 window yielded a marginally significant main effect of T1 accuracy, $t_{10} = 2.2$, $p = .051$; there was no reliable main effect in the P2 window ($p = .41$).
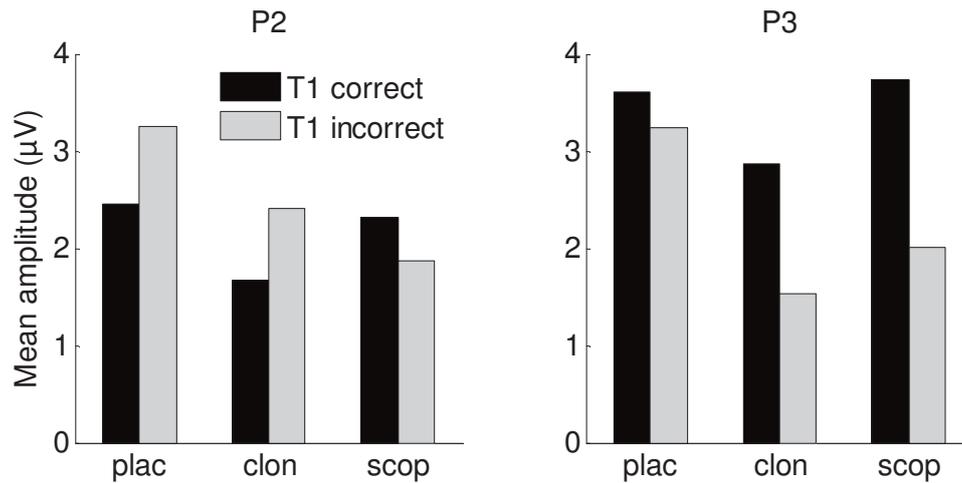
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Figure 3.4. Mean average amplitude in the P2 and P3 windows as a function of treatment and T1 accuracy.

3.4 Discussion

In the present research we investigated the effects of clonidine and scopolamine on multiple target detection in an RSVP context. In line with Nieuwenhuis et al. (2007), we found no effect of treatment on the attentional blink for T2. In contrast, we found that both clonidine and scopolamine impaired T1 accuracy. For clonidine, this effect was accompanied by a significant reduction in T1-evoked P2 and P3 amplitude.

The current study replicated Nieuwenhuis et al. (2007) with two design improvements: a crossover design instead of a between-subject design; and a higher dose of clonidine, although, after a clinically relevant drop in blood pressure in one participant, the final 7 participants were given the clonidine dose that was used by Nieuwenhuis et al. (2007). Like Nieuwenhuis et al. (2007), we found no effect of clonidine on the attentional blink, which poses a challenge for

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the attentional blink theory of Nieuwenhuis et al. (2005b) under the assumption that clonidine affects the phasic LC response. However, the evidence that addresses this assumption is limited. As in the present study, clonidine has been found to attenuate the amplitude of the P3 (Joseph & Sitaram, 1989), which has been proposed to reflect phasic LC activity (Nieuwenhuis et al., 2005a). Furthermore, the suppressive effect of clonidine on tonic LC activity (e.g., Abercrombie & Jacobs, 1987; Adams & Foote, 1988), along with the reported interaction between tonic and phasic activity of the LC (Aston-Jones & Cohen, 2005), suggests that clonidine may also affect sensory-evoked LC responses. However, the only study that we are aware of that directly examined this issue found mixed results: Adams and Foote (1988) found that during the onset of clonidine-induced suppressed LC firing, LC responses to sensory (footshock) stimuli were relatively preserved, although later during the experiment the reliability of sensory-evoked LC responses was greatly reduced. Furthermore, previous work from our lab has failed to find evidence that clonidine modulated the phasic alerting response to a task-irrelevant, auditory ("accessory") stimulus, despite it having an effect on general alertness (Brown et al., 2015). Thus, we may not have found an effect of clonidine on the attentional blink because it is possible that phasic LC responses to RSVP targets were preserved.

Alternatively, if clonidine affects the phasic LC response, as the observed reduction in T1-evoked P3 amplitude might indicate, the theory of Nieuwenhuis et al. (2005b) could be incorrect. For example, the size and the duration of the LC refractory period, which is purportedly mirrored in the attentional blink, may not be proportional to the size of the phasic LC response, as the theory suggests. Or noradrenaline may not be involved in the attentional blink at all. At first sight, the study by de Martino et al. (2008) suggests a role of the noradrenergic system in the attentional blink: these authors found that administration of the β-adrenoceptor antagonist propranolol decreased T2 accuracy, while administration of the noradrenergic reuptake inhibitor reboxetine increased accuracy for emotional T2

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stimuli. However, the authors found no interactions between lag and treatment, and in one of their experiments propranolol impaired T1 accuracy as well. Taken together, these findings suggest that propranolol and reboxetine do not specifically modulate the attentional blink, but target detection under RSVP conditions in general. More convincing evidence for noradrenergic modulation of the attentional blink was provided by Jepma et al. (2011), who studied patients with dopamine-β-hydroxylase deficiency, a rare genetic syndrome characterized by the complete lack of noradrenaline. They found that these patients had a larger attentional blink than healthy controls, and that this impairment was restored by treatment with a synthetic precursor for noradrenaline. Although these findings pose a challenge for the theory of Nieuwenhuis et al. (2005a), which explains the attentional blink as a byproduct of phasic noradrenaline release in the LC, they are generally consistent with a role for noradrenaline in the attentional blink. Recent studies have also reported evidence that decreased levels of dopamine in the striatum are associated with a larger attentional blink (Colzato, Slagter, de Rover, & Hommel, 2011; Colzato, Slagter, Spapé, & Hommel, 2008; Slagter et al., 2012). Other neurotransmitters may hence also play a role in the attentional blink.

In our study, clonidine had a clear detrimental effect on T1 identification accuracy. Presumably, clonidine impaired performance by reducing general alertness (e.g., Brown et al., in press; Coull, Frith, Dolan, Frackowiak, & Grasby, 1997; Coull, 2001; Smith & Nutt, 1996), a possibility that is supported by the negative effects of clonidine on SRT, and the fact that scopolamine, which also increased SRT, similarly reduced T1 identification accuracy. Nieuwenhuis et al. (2007) did not find a significant effect of clonidine on T1 accuracy. However, in their study, all participants took the lower clonidine dose, and their effect was in the same direction and of a similar magnitude (5%) as the effect we observed here (6%). To further understand the effect of clonidine on T1 accuracy, we examined T1-related ERP waveforms (Kenemans & Kähkönen, 2011).

Clonidine attenuated the amplitude of the T1-evoked P2 and P3 components. The functional significance of the P2 is relatively ill-defined, but it has been related to some aspect of stimulus classification (reviewed in Key, Dove, & Maguire, 2005). The opposite seems to apply for the P3: since its discovery in 1965, a number of theories have been proposed to account for its functional significance. In the context of the current paper, the work by Nieuwenhuis et al. (2005a) is particularly relevant, as these authors conceptualized the P3 as reflecting phasic noradrenergic activity and the concomitant increase in neural gain. As noted above, the clonidine-related decrease in P3 amplitude is consistent with several previous studies (Nieuwenhuis et al., 2005a; Joseph & Sitaram, 1989). In contrast, previous studies have reported no effect of clonidine on the amplitude of the P2 (Abuljawad, Langley, Bradshaw, & Szabadi, 2001; Turetsky & Fein, 2002). We propose that the effects of clonidine on T1-evoked P2 and P3 amplitudes and corresponding behaviors were mediated by a general decrease in alertness.

If clonidine reduced general alertness, why is that not manifested in reduced overall T2 accuracy? Relatedly, why did clonidine reduce lag-1 sparing? We propose that the perception of T1 caused a phasic alerting response that temporarily compensated for the drug-induced decrease in tonic alertness. As we have shown in other work, drug-related reductions in alertness yield room for compensatory accessory stimulus-induced performance improvements (Brown et al., in press). In a similar vein, Smith and Nutt (1996) found that arousal evoked by white noise can reduce the frequency of attentional lapses induced by clonidine intake. Furthermore, we propose that this phasic alerting response takes some time to unfold. This is suggested by our finding that the drug-related impairments in T1 accuracy extended to T2 accuracy if T2 was presented immediately after T1 (i.e. at lag 1). Only after that, from lag 2 onward, did accuracy return to placebo levels.

The scopolamine findings show a remarkable similarity to the clonidine findings. Like clonidine, scopolamine reduced T1 accuracy without having a clear

effect on T2 accuracy. The reduction in T1 accuracy is generally consistent with a number of studies that have reported scopolamine-induced attentional impairments, as indicated by impaired performance in sustained attention tasks (Hasselmo & Sarter, 2011). Scopolamine also led to reduced amplitudes of the P2 and P3 relative to placebo, although these reductions were not statistically significant.

It is possible that the effects of clonidine and scopolamine on behavior and ERP waveforms, though similar, were achieved via largely independent neural pathways, that both affect general alertness. However, we believe it is more plausible that the similar effects of these two drugs in the current study and another recent study in our lab (Brown et al., 2015) reflect interactions between the two neuromodulator systems involved (Briand, Gritton, Howe, Young, & Sarter, 2007). On the one hand, acetylcholine has been demonstrated to activate LC neurons in rats and co-administration of scopolamine reduces this effect (Egan & North, 1985; Adams & Foote, 1988). Egan and North proposed that scopolamine antagonizes muscarinic receptors in the LC, leading to reduced noradrenergic baseline activation. On that assumption, both clonidine and scopolamine may have reduced noradrenergic baseline activity, leading to a similar pattern of results for both treatments. On the other hand, there is solid evidence that clonidine inhibits cortical ACh release (Acquas, Wilson, & Fibiger, 1998), probably via α_2 receptors in the basal forebrain (cf. Dringenberg & Vanderwolf, 1998). This suggests that both clonidine and scopolamine may have reduced basal forebrain activity and consequent release of acetylcholine, thus leading to a similar pattern of results. The current data underline the importance of studying interactions between the noradrenergic and cholinergic neuromodulator systems in regulating temporal fluctuations in attention.