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

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4. Noradrenergic and cholinergic effects on speed and ensitivity measures of phasic alerting

Abstract

An intense but task-irrelevant auditory accessory stimulus that is presented almost simultaneously with a visual imperative stimulus can reduce reaction times to that stimulus. The information-processing locus and neural underpinnings underlying this phasic alerting effect are still poorly understood. We investigated a possible noradrenergic or cholinergic basis of the accessory stimulus effect in a double-blind pharmacological study (N=18), in which healthy participants received a single dose of clonidine (an α_2–adrenergic agonist), scopolamine (a muscarinic antagonist) and placebo in separate test sessions. A backward-masking procedure was employed to examine, for the first time, the effect of accessory stimuli on perceptual sensitivity. We found that accessory stimuli enhanced perceptual sensitivity and decreased reaction times to target stimuli, consistent with a recent hypothesis that phasic alerting speeds up stimulus encoding. In contrast to our expectations, clonidine increased the accessory stimulus effect, a finding that seems at odds with earlier proposals that phasic alerting effects are mediated by a phasic noradrenergic response. Furthermore, the accessory stimulus effect was modulated to a similar extent by clonidine and scopolamine, suggesting that the effect of clonidine was not specific to the noradrenergic system. Our results instead suggest that clonidine and scopolamine decrease general alertness, and that these drug-related reductions in alertness yield room for compensatory performance improvements by phasic alerting.

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4.1 Introduction

An auditory *accessory* stimulus (AS), an intense but task-irrelevant sound that is presented almost simultaneously with a visual imperative stimulus, can reduce choice reaction times to that stimulus even though it contains no information about the correct response (Bernstein, Clark, and Edelstein, 1969a; 1969b). It has been demonstrated that an auditory AS can even speed up a response when it immediately *follows* a visual imperative stimulus (Morrell, 1968). Studies of the AS effect can significantly contribute to our understanding of temporal fluctuations in attention. However, although several studies have begun to unravel the mechanisms underlying the AS effect, it remains uncertain which stage of the information processing stream is precipitated by an AS, and the neural basis of this effect is poorly understood. We performed an experiment to ascertain the information processing locus of the AS effect, as well as to study the neuromodulatory basis of the AS effect.

Various theories have been proposed to account for the information processing locus of the AS effect. For example, it has been suggested that the presentation of an AS speeds up the decision-making process. Decision-making has been conceptualized as the accumulation of noisy data until the threshold for a given response is reached and the concomitant response is executed (Gold & Shadlen, 2007; Smith & Ratcliff, 2004). It has been suggested that an AS might speed up responses either by lowering the decision threshold (Posner, 1978) or by increasing the rate at which evidence is accumulated (Hackley & Valle-Inclán, 1999). An alternative account suggests that the presentation of an AS affects motor execution, a later stage of information processing. This hypothesis is based on findings that response force increases (Stahl & Rammsayer, 2005; Miller, Franz, & Ulrich, 1999) and reflexes are sped up on AS trials (Low, Larson, Burke, & Hackley, 1996; Stafford & Jacobs, 1990). Yet another theory suggests that an AS influences stimulus encoding. This account is based on the assumption of

multisensory integration: presenting an auditory AS is thought to increase the subjective intensity of a visual imperative stimulus (Bernstein, Rose, & Ashe, 1970), thereby facilitating encoding, and thus resulting in a faster response.

Recently, Jepma, Wagenmakers, Band, and Nieuwenhuis (2009) demonstrated that the early visual P1 component of the event-related potential that is evoked by imperative stimuli is larger on AS trials, providing evidence for this so-called energy integration hypothesis. Furthermore, in a diffusion-model analysis, these authors demonstrated that the parameter that reflects the duration of nondecision processes was smaller on AS trials, whereas parameters that reflect evidence accumulation and response threshold levels were not affected. These findings, together with electrophysiological evidence that an AS speeds up processes prior to motor preparation (Hackley & Valle-Inclán, 1998), provide important evidence that an AS may influence early encoding instead of motor execution or decision-making processes. Converging evidence for an effect of temporal attention on the duration of stimulus encoding has been obtained in foreperiod paradigms: shorter or validly cued foreperiods, conditions of relatively low uncertainty about the timing of the upcoming imperative stimulus, were associated with a decreased nondecision time, but low temporal uncertainty did not affect either evidence accumulation rate or the decision threshold (Jepma, Wagenmakers, and Nieuwenhuis, 2012). These findings suggest that both exogenous (AS effect) and endogenous (foreperiod effect) changes in temporal attention influence the stimulus encoding stage of information processing.

In the present study, we performed a psychophysical experiment to test the hypothesis that the AS effect influences the encoding stage of information processing. Our cognitive task was based on that used by Rolke and Hofmann (2007), who found that reducing temporal uncertainty about the onset of an imperative stimulus led to increased perceptual sensitivity. This finding corroborates the hypothesis that accessory stimuli speed up the encoding stage of information processing. Following Rolke and Hofmann (2007), our participants

had to detect a small opening on either side of a backward-masked square stimulus. On half of the trials the visual imperative stimulus was accompanied by an auditory AS. Although this design does not allow us to distinguish between encoding and rate of evidence accumulation as loci of the AS effect (cf. Rolke & Hofmann, 2007), it can nevertheless provide a first demonstration of an AS effect on perceptual sensitivity.

Another important question that remains, concerns the neuromodulatory underpinnings of the AS effect. Witte and Marrocco (1997) investigated the effect of pharmacological modulation of noradrenergic activity on the alerting effect in rhesus monkeys. Monkeys were trained to respond as quickly as possible to a visual target stimulus that was occasionally preceded by a visual alerting stimulus that provided no information about the correct response. Cue-target interval was systematically varied (100, 400, 700 ms), with the shortest interval being similar to AS-target intervals in typical AS studies. Attenuation of noradrenergic activity by administration of clonidine (see below) and to a lesser extent guanfacine, significantly reduced the size of the alerting effect in a dose-dependent fashion. This effect of drug was similar across cue-target intervals. These findings suggest that the AS effect may be mediated by the noradrenergic system. Converging evidence for this view is provided by studies in humans that have linked noradrenergic functioning to other measures of temporal attention such as the temporal-cuing effect (Coull, Nobre, & Frith, 2001), vigilant attention (Langner & Eickhoff, 2013) and the attentional blink (Jepma, Deinum, Asplund, Rombouts, Tamsma, Tjeerdema, Spape, Garland, Robertson, Lenders, & Nieuwenhuis, 2011; De Martino, Strange, & Dolan, 2008); and by a study showing that AS-related facilitation of a monosynaptic reflex in cats can be diminished or blocked by antagonism or destruction of the noradrenergic input to the motor system (Stafford & Jacobs, 1990).

To gain further insight in the involvement of the noradrenergic system in the AS effect, we tested healthy adult participants in a placebo-controlled

randomized crossover design with clonidine. Clonidine is a centrally acting α_2 agonist that attenuates baseline noradrenergic activity by agonizing pre-synaptic α_2 autoreceptors, and decreases the amplitude of the human P3 component, an electrophysiological correlate of phasic noradrenaline release (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Pineda, Foote, & Neville, 1989). If the AS effect is subserved by a phasic response of the noradrenergic system, attenuating activity of that system ought to reduce or even abolish the AS effect.

While several studies have investigated the effects of cholinergic nicotinic agents on temporal alerting (Beane & Marrocco, 2004; Stewart, Burke, & Marrocco, 2001), little is known about the involvement of the cholinergic muscarinic system in temporal attention. In a third condition, we administered scopolamine, a muscarinic antagonist that has a similar sedative profile as clonidine, to gain more insight in the role of the cholinergic system in temporal attention, and to test whether modulation of the AS effect by clonidine reflects involvement of the noradrenergic system or reflects iatrogenic sedation.

4.2 Methods

4.2.1.Participants

Eighteen healthy young adult students (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 and a diastolic blood pressure above 70 mmHg and a heart frequency over 65 beats per minute in rest were included in the study. All participants underwent a medical screening which included a routine physical examination; only healthy persons were allowed to participate. Participants took no prescribed medication and did not smoke. 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. For safety reasons, the dose of clonidine was reduced to 150 µg for the final seven participants. Preliminary analyses revealed comparable effects for these dosages, so in the analyses reported below they 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. Informed consent was obtained from all participants prior to inclusion in the study.

4.2.2. Task

Participants performed a psychophysical version of the accessory stimulus (AS) task, modeled after Rolke and Hofmann (2007). Each trial started with a 500-ms fixation point (black plus sign on a white background, visual angle 0.4 x 0.4°), followed by a target, a black square (0.18 x 0.18°) with a small opening (0.4 x 0.4°) on either the left or the right side, presented for 32, 48, or 64 ms. The square was masked by a visual patch of random noise, which remained on-screen until the response (with a maximum of 4 s). Participants were instructed to respond with a button press ipsilateral to the side of the opening in the square. The mask stimulus was followed by a blank screen that lasted 2, 3, or 4 seconds. One of three different random noise patches was randomly presented during each trial. To keep participants' attention focused on the center of the screen, all stimuli were presented within a square frame (3.9 x 3.9°). On a random 50% of all trials, a loud noise ('accessory stimulus', 800 Hz, 72 dB(A)) was presented for 150 ms: the sound started 30 ms prior to the onset of the target stimulus.

The task consisted of 384 trials, divided over 8 blocks of 48 trials each. In the first test session, the difficulty of the task was adjusted on-line to keep participants' performance away from ceiling and chance levels of performance: at the end of each block, if the participants' accuracy was below 60%, easier target stimuli (i.e. squares with larger openings) were used in the next block; if accuracy

was above 75%, more difficult target stimuli (i.e. with smaller openings) were used in the next block. In total, three stimulus sets of varying difficulty were available, and the first block always started with the easiest target stimuli (i.e. largest openings). For every participant, the difficulty settings were kept constant over the three test sessions. The task was preceded by a practice block of 12 trials, in which feedback on performance was given after every response.

4.2.3 Procedure

Participants were instructed to abstain from caffeine, alcohol, and all psycho-active substances from 15h prior to the start of each session. 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 administration at different times prior to testing. This double-dummy design resulted in one clonidine session (i.e. clonidine verum and scopolamine placebo), one scopolamine session (clonidine placebo and scopolamine verum), and one placebo session (clonidine and scopolamine placebos). To eliminate the confound of treatment order, we stratified this factor by distributing the six possible treatment orders evenly across participants.

At the start of each session (t = -20), a peripheral intravenous cannula was placed and connected to an IV normal 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 ECG monitor. Blood pressure and heart rate were then measured, and measures of participant alertness were obtained: participants completed a simple reaction time (SRT) task, in which they 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. To

measure the sedative properties of clonidine and scopolamine, we administered the SRT task upon a participant's arrival in the lab, as well as right before and after the participant performed the AS task.

At t = 0, 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, participants ingested a microcrystalline cellulose-filled capsule with either scopolamine or placebo.

At t = 90, participants performed the AS task, as part of a larger test battery of which the results are not reported here. The task lasted approximately 30 mins. 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.

4.2.4. Analyses

To test for AS effects on perceptual sensitivity and response speed, we submitted *d'* and reaction time (RT) data to 3 (treatment) × 3 (target presentation duration) × 2 (AS presence) repeated-measures analyses of variance (ANOVAs). *d'* was computed as z(proportion of hits)—z(proportion of false alarms; Stanislaw & Todorov,1999). Greenhouse-Geisser corrections were applied whenever the assumption of sphericity was violated; in such cases, uncorrected degrees of freedom are reported. To examine noradrenergic and cholinergic modulations of the AS effect, we submitted *d'* and RT data to a 3 (treatment) × 3 (imperative stimulus presentation duration) × 2 (AS presence) repeated-measures multivariate analysis of variance (MANOVA). Trials were excluded from analysis if an RT fell below or above 2 standard deviations of a given participant's standardized mean RT.

4.3 Results

4.3.1. Physiological and alertness data

Figure 4.1A shows that 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 AS task (t = 90-120). The difference in systolic and diastolic blood pressure between placebo and scopolamine was not significant. Figure 4.1B shows that scopolamine (67/min) lowered heart frequency relative to placebo (72/min) and clonidine (72/min), also during (t = 105) and right after (t = 120) task performance.

Results from the SRT task, administered at baseline (arrival of participant), right before, and right after performing the AS task, suggest that clonidine increased SRT (306 ms) relative to placebo (275 ms) and scopolamine (291 ms), $F(2, 34) = 10.4$, $p < .0005$, partial $\eta^2 = .38$. Furthermore, mean SRT increased as the test session progressed, $F(2, 34) = 17.8$, $p < .0005$, partial $\eta^2 = .51$. As depicted in Figure 4.1C, clonidine increased SRT more strongly as the test session progressed than scopolamine and placebo, $F(4, 68) = 5.3$, $p = .007$, partial $\eta^2 = .24$. Pairwise comparisons for pre-test and post-test indicated that clonidine reliably differed from placebo and scopolamine during the pre-test, and that both clonidine and scopolamine reliably differed from placebo during the post-test.

4.3.2. Effect of AS on reaction times and perceptual sensitivity

As expected, trials that were accompanied by an AS were associated with shorter RTs (576 ms) than trials that were not accompanied by an accessory stimulus (noAS trials; 621 ms), $F(1, 17) = 54.5$, $p < .0005$, partial $\eta^2 = .76$ (see Figure 4.2, left panel). RTs decreased with increasing target presentation duration, $F(2, 34) = 37.1$, $p < .0005$, partial $\eta^2 = .69$. There was no interaction between AS presence and target presentation duration ($p = .55$).

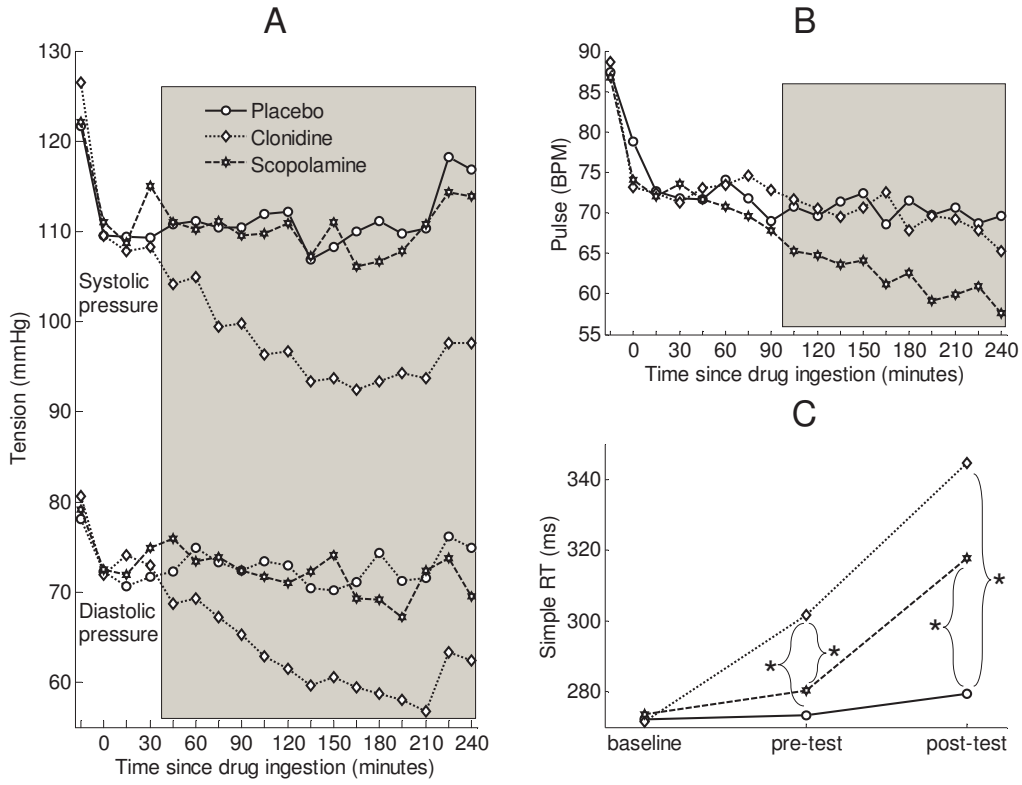

Figure 4.1A. Blood pressure data for the three treatments. The shaded grey area indicates significant pairwise comparisons between clonidine and placebo ($p < .05$). B. Heart frequency for the three treatments. The shaded grey area indicates significant pairwise comparisons between scopolamine and placebo ($p < .05$). 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 AS task. All pairwise comparisons accompanied by an asterisk were significant ($p < .05$).

Importantly, we obtained similar results for perceptual sensitivity (Figure 4.2, right panel). AS trials were associated with increased perceptual sensitivity (d' = 1.61) relative to noAS trials (d' = 1.51), $F(1, 17) = 11.2$, $p = .004$, partial $\eta^2 = .40$. Furthermore, perceptual sensitivity increased with target presentation duration, $F(2, 34) = 80.3$, $p < .0005$, partial $\eta^2 = .83$. There was no interaction between AS presence and target presentation duration ($p = .22$).

4.3.3. Effect of treatment on AS effect

As can be seen in Figure 4.3, clonidine was associated with the lowest perceptual sensitivity (*d'* = 1.31) and longest RTs (639 ms), followed by scopolamine (*d'* = 1.50; RT = 601 ms), and placebo (*d'* = 1.86; RT = 557 ms). This pattern was expressed in a significant main effect of treatment in the repeated-measures MANOVA, Wilks' lambda = .51, $F(4, 14) = 3.3$, $p = .04$, partial $\eta^2 = .49$.

Crucially, we found an interaction between treatment and AS presence, Wilks' lambda = .42, $F(4, 14) = 4.8$, $p = .01$, partial $\eta^2 = .58$. Follow-up pairwise comparisons between the treatments indicated that clonidine was associated with a greater AS benefit (RT AS – noAS = -65 ms, *d'*AS – noAS = 0.18) than placebo (RT difference = -29 ms, *d'* difference = 0.02; Wilks' lambda = .44, $p = .001$). Scopolamine also increased the AS effect compared to placebo (RT difference = -43 ms, *d'* difference = 0.13), but not reliably so, Wilks' lambda = .89, $p = .41$). The AS effects for scopolamine and clonidine also did not reliably differ, Wilks' lambda = .86, $p = .31$.

Figure 4.3 also shows that there was no AS effect on *d'* in the placebo condition; the significant main effect of AS presence in the *d'* ANOVA reflected the AS effects observed in the two drug conditions.

4.4 Discussion

4.4.1. Accessory stimuli enhance perceptual sensitivity

We have provided a first demonstration, using psychophysics, of an AS effect on perceptual sensitivity. Accessory stimuli in our location-discrimination task with backward-masking not only speeded up RTs—the typical finding in AS studies—but also increased *d'*, a signal-detection measure of perceptual sensitivity. These *d'* findings can be explained by two different hypotheses (cf. Rolke & Hofmann, 2007). According to one hypothesis, an AS reduces the time needed for target

encoding so that evidence accumulation can start earlier and accumulated evidence can increase to a higher level before the target is masked.

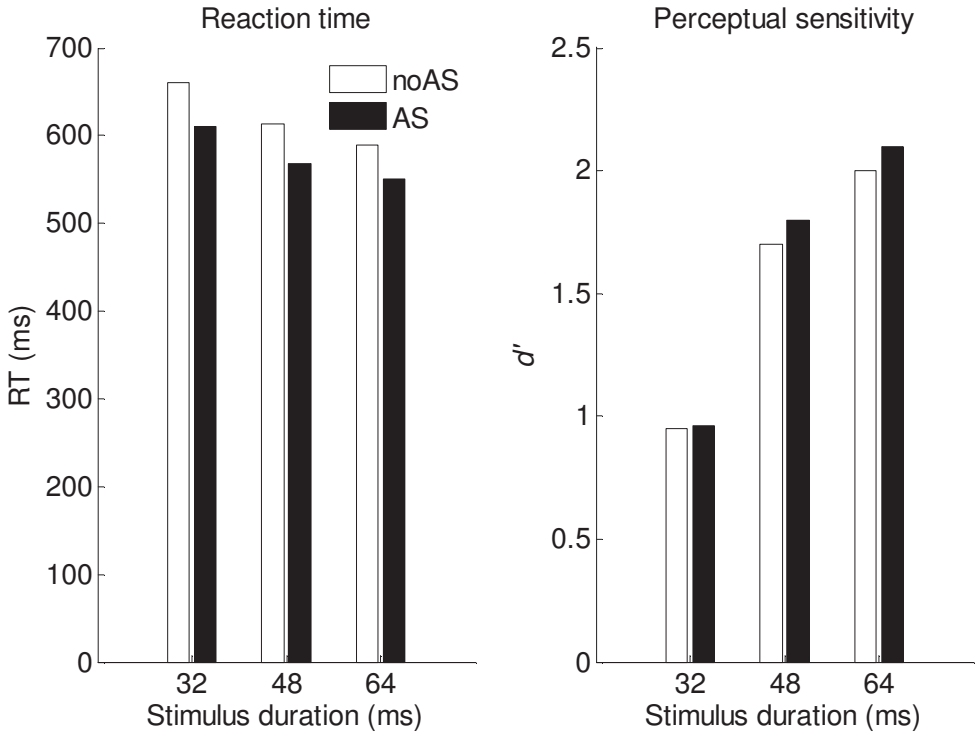

Figure 4.2A. AS effect on RT for every target presentation duration. B. AS effect on *d'* for every target presentation duration.

We will refer to this model as the early onset hypothesis (Nieuwenhuis & de Kleijn, 2013; Seifried, Ulrich, Bausenhart, Rolke, & Osman, 2010). According to the other hypothesis, an AS increases the rate (as opposed to the onset) of evidence accumulation, so that more evidence can be accumulated before the target is masked. Although the present study cannot arbitrate between these two hypotheses, other literature strongly favors the early onset hypothesis (Jepma et al., 2009). Thus, our study supports previous work that suggests that the AS effect is rooted in the encoding stage of information processing.

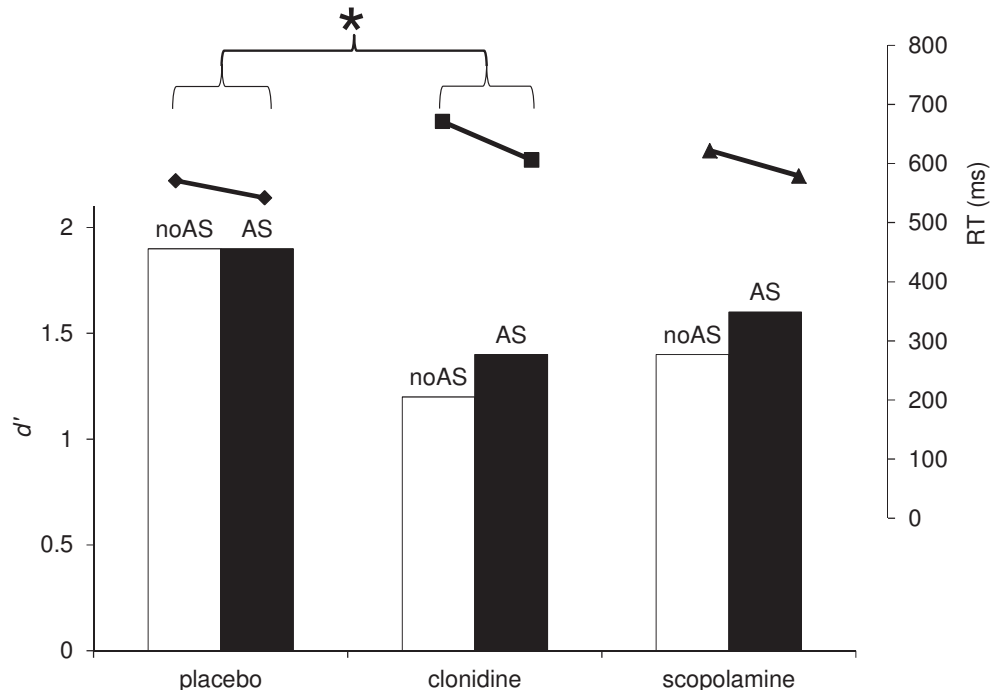

Figure 4.3. Effect of treatment and AS presence on *d'* (bars) and RT (lines). Asterisk indicates significantly larger AS effect after clonidine than after placebo treatment (p = .01).

The fact that we only found an AS effect on perceptual sensitivity in the two drug conditions begs the question why this effect was not present in the placebo condition. Indeed, our findings in the placebo condition do not replicate Rolke and Hofmann (2007), who found that increased temporal attention enhanced perceptual sensitivity in the same task. Admittedly, the AS paradigm differs considerably from the constant-foreperiod paradigm used by Rolke and Hofmann (2007). In the AS paradigm, temporal attention is increased mainly by phasic alerting, whereas in the foreperiod paradigm, improvements in performance are caused by controlled temporal attention shifts and/or associative learning between the warning signal and the imperative stimuli (Capizzi, Sanabria, & Correa, 2012; Steinborn, Rolke, Bratzke, & Ulrich, 2010). However, in earlier work (Jepma et al., 2009, 2012), we found that these modulations of temporal attention influence RT

and accuracy in the same manner: by reducing the time required for stimulus encoding. So why did we not replicate the findings of Rolke and Hofmann?

We hypothesize that the AS effect on perceptual sensitivity is only manifested in conditions that are associated with suboptimal alertness. This notion is consistent with literature that suggests that the AS effect on RT is relatively small under conditions of low temporal uncertainty (Hackley et al., 2009; Sanders, 1980). Our placebo condition was probably associated with a state of relatively high alertness, especially around the time of the AS, because the onset of the AS could be predicted using a fixation cross that preceded the AS by a fixed time interval. In contrast, in Rolke and Hofmann (2007), the onset of the warning cue was not predictable, and therefore subjects were presumably less alert when the warning cue was presented. In the current study, the clonidine and scopolamine conditions were clearly associated with reduced general alertness, as indicated by increased SRTs and impaired overall performance in the location-discrimination task. We hypothesize that AS-triggered phasic alerting temporarily compensated for this reduction in alertness, resulting in a pronounced AS effect in the drug conditions. In line with this view, it has been demonstrated that an auditory warning cue enhances performance to visual stimuli in patients with right hemisphere neglect, a condition characterized by decreased tonic alertness (Robertson, Mattingly, Rorden, & Driver, 1998).

In conclusion, we found a reliable AS effect on perceptual sensitivity, in line with the hypothesis that the AS effect has a locus in the encoding stage of information processing (Jepma et al., 2009). Although the literature suggests that accessory stimuli also affect motor processes (Hackley & Valle-Inclán, 2003), as manifested in such parameters as response force, this effect does not contribute to the speeding up of RTs (Jepma et al., 2009; Hackley & Valle-Inclán, 1998).

4.4.2. The AS effect is not mediated by a phasic noradrenergic response

We found a clear effect of clonidine on the AS effect, consistent with the general notion of an important role for noradrenaline in temporal attention. However, in contrast to our expectations, clonidine increased the AS effect, a finding that is incompatible with the hypothesis that phasic alerting effects such as the AS effect are mediated by a phasic noradrenergic response (Fernandez-Duque & Posner, 1997; Hackley & Valle-Inclán, 2003). Furthermore, the AS effect was modulated to a similar extent by clonidine and scopolamine, suggesting that the effect of clonidine was not specific to the noradrenergic system. As proposed above, our observations instead suggest a general alertness explanation of our findings: drug-related reductions in alertness yield room for compensatory AS-induced performance improvements. In a related vein, arousal evoked by white noise (Smith & Nutt, 1996) and caffeine consumption (Smith, Brice, Nash, Rich, & Nutt, 2003) has been found to remove many of the cognitive performance impairments caused by clonidine intake. This suggests that other, tonic alerting manipulations can also counteract the effects of clonidine on general alertness. This effect might be mediated by increased crosstalk between attention-related brain areas during periods of high arousal, which might counteract the deteriorating effects of clonidine (Coull et al., 2001).

Clonidine, the "prototype α_2 agonist" (Wecker, Crespo, Dunaway, Faingold, & Watts, 2010), has been around for almost 50 years (Stähle, 2000). It is still widely prescribed; current indications include hypertension, attention-deficit/hyperactivity disorder, and menopausal hot flushes. The drug is also used as an adjuvant in opiate withdrawal treatment. Therefore, the above observations that exogenous auditory cues and tonic alerting manipulations can compensate clonidine-induced attentional impairments seem particularly relevant. More in general, our findings have significant implications for research in both the neuropsychological domain and the ergonomic and human-factors domain, since

they demonstrate that exogenous stimulation may be capable to compensate impairments in endogenous alertness.

Acetylcholine has been suggested to play a key role in attention, but to date most studies have focused on the nicotinic cholinergic receptor class (for a review, see Beane & Marrocco, 2001). The nicotinic system appears to be involved in regulating spatial attention but seems to have no role in alerting (e.g., Stewart, Burke, & Marrocco, 2001; Thiel, Zilles, & Fink, 2005; Witte, Davidson, & Marrocco, 1997). Our study is among the first to study the involvement of the muscarinic cholinergic receptor class in temporal attention. We found no difference between AS effects in the scopolamine and placebo conditions, suggesting that muscarinic receptors do not play an important role in phasic alerting.

Our data do not support the hypothesis that phasic noradrenaline responses mediate the AS effect, so we briefly consider two alternative hypotheses. As discussed in the introduction, the energy integration account explains the AS effect in terms of energy integration of the auditory AS and visual imperative stimulus across sensory modalities. This increases perceived intensity of the imperative stimulus and reduces RTs. The mechanism responsible for translating the additional energy into enhanced performance may be stochastic resonance. Stochastic resonance refers to the phenomenon that the addition of noise to a nonlinear system can enhance its response to a weak input signal (Benzi, Sutera, & Vulpiani, 1981). The AS effect could be a manifestation of stochastic resonance: by adding noise (the AS) to a subthreshold imperative stimulus, the intensity of that stimulus is boosted to a supra-threshold level, which facilitates its encoding and reduces ensuing RTs (cf. Moss, Ward, & Sannita, 2004). The neural substrate of this effect might be increased responsiveness of multisensory neurons to the combined energy of the AS and imperative stimulus (Manjarrez, Mendez, Martinez, Flores, & Mirasso, 2007).

Another explanation of the AS effect is provided by the phase reset hypothesis, which assumes that the AS disrupts ongoing neural oscillations so as to

synchronize their phase (Diederich, Schumburg, & Colonius, 2012). The presentation of an AS is hypothesized to reset neural oscillations to their ideal phase; stimuli following the AS, presented during this ideal phase, evoke amplified responses, while stimuli presented outside this phase are suppressed (Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007; Kayser, Petkov, & Logothetis, 2008). Work with saccadic RTs to visual stimuli preceded by an auditory AS provides evidence for this hypothesis (Diederich et al., 2012). More in general, this evidence is consistent with other studies that claim an important role for phase entrainment in temporal expectation effects (Stefanics et al., 2010; Cravo, Rohenkohl, Wyart, & Nobre, 2013).

It is important to note that α_2 agents like clonidine can have both pre- and postsynaptic effects (Samuels & Szabadi, 2008). Predominantly presynaptic stimulation of α_2 receptors leads to attenuation of noradrenergic activity and decreased arousal, while predominantly postsynaptic stimulation of α_2 receptors leads to increased noradrenergic activity and increased arousal (Samuels & Szabadi, 2008). Indeed, clonidine can both enhance and deteriorate task performance in monkeys, an effect that has been suggested to depend on the dose of clonidine that was administered (Witte & Marrocco, 1997). We found an enhanced AS effect following clonidine administration, which at first blush seems to suggest a predominance of postsynaptic α_2 stimulation and concomitant increase in arousal. However, low doses of clonidine as used in our study are generally assumed to act predominantly presynaptically (Frith, Dowdy, Ferrier, & Crow, 1985; Coull, Middleton, Robbins, & Sahakian, 1995a/1995b; Coull et al., 1995c; Jäkälä et al., 1999). Furthermore, our participants exhibited clear signs of sedation (as reflected by SRTs), which is a common side effect of presynaptic α_2 stimulation, an effect that is subserved by inhibition of wakefulness-inducing histaminergic pathways due to "switching off" of LC neurons (Samuels & Szabadi, 2008).

Our study is the first to demonstrate an AS effect on perceptual sensitivity, and we have provided evidence that argues against a phasic noradrenergic mechanism mediating the AS effect in humans. Further work, including a replication study with larger sample size, will be necessary to better understand the neural underpinnings of the AS effect.