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Noradrenergic and cholinergic modulation of late ERP responses to deviant stimuli

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Abstract

Researchers have proposed several hypotheses about the neuromodulator systems involved in generating P3 components of the ERP. To test some of these hypotheses, we conducted a randomized placebo-controlled crossover study in which we investigated how the late positive ERP response to deviant stimuli is modulated by (a) clonidine, an α_2 agonist that attenuates baseline noradrenergic activity; and (b) scopolamine, a muscarinic antagonist of acetylcholine receptors. We collected EEG data from 18 healthy volunteers during the performance of an auditory oddball task with several active and passive task conditions. We then used temporospatial principal component analysis (PCA) to decompose the ERP waveforms. The PCA revealed two distinct late positive ERP components: the classic parietal P300 and the frontal novelty P3. Statistical analysis of the temporospatial factor scores indicated that in most conditions the amplitude of the classic P300 was increased by clonidine and scopolamine. In contrast, the amplitude of the novelty P3 was decreased by both drugs. The similar pattern of results for clonidine and scopolamine probably reflects the strong interactions between the noradrenergic and cholinergic systems. The results, in combination with previous pharmacological studies, suggest a critical role for both neuromodulator systems in the generation of the P300 and the novelty P3.

Descriptors: Cognition, Pharmacology, EEG

The P300 to task-relevant stimuli has undoubtedly been the most intensively studied component of the EEG. It is ubiquitous in stimulus-related, scalp-recorded, and intracranial EEG activity, it is sensitive to a wide range of variables and states, including attention, expectation, and value (Johnson, 1986), and it has been proposed as a biomarker of a large array of brain disorders (Polich, 2004). Furthermore, the P300 has been proposed to reflect key aspects of cognitive function, including evidence accumulation for perceptual decisions (O'Connell, Dockree, & Kelly, 2012; Verleger, Jaskowski, & Wascher, 2005), memory updating (Donchin & Coles, 1988; Nieuwenhuis, 2011), and potentiation of responses to motivationally significant stimuli (Nieuwenhuis, Aston-Jones, & Cohen, 2005). The classic P300 can be distinguished from two potentially related late ERP components, with a more frontal scalp distribution and somewhat earlier latency, both of which have been described as a central nervous system component of the orienting response: the novelty P3, which is elicited by attended highly salient deviants or novel stimuli (Friedman, Cycowicz, & Gaeta, 2001; Yamaguchi & Knight, 1991), and the P3a, which is elicited by simple task-irrelevant deviants (Polich, 2007; Squires, Squires, & Hillyard, 1975).[1] However, it is still unclear whether the P300 (or P3b), novelty P3, and P3a only happen to share some characteristics (e.g., latency range, polarity) but do in fact reflect independent underlying neural processes, or whether they reflect the same underlying process operating in different brain areas under different circumstances.

A powerful way to address this question is to investigate the neurochemical basis of these ERP components. Examining whether these late ERP responses reflect distinct or common neuromodulatory actions in the cortex can be informative both about the relationship between the components and about the functional significance of underlying neural activity. Researchers have proposed several theories about the neuromodulator systems involved in generating the P300 and related components. Although there is some consensus that the noradrenergic system plays a critical role in generating the classic P300 (Nieuwenhuis et al., 2005; Polich, 2007; Ranganath & Rainer, 2003), there are several competing views about the origin of the novelty P3 and/or P3a, with different theories proposing a key role for norepinephrine (Nieuwenhuis

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1. As we will discuss below, some have argued that the novelty P3 and P3a reflect the same component.

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et al., 2005), dopamine (Polich, 2007), and acetylcholine (Ranganath & Rainer, 2003). Although these theories are based on a variety of neuroscientific findings, they are primarily based on acute pharmacological challenge studies in humans and nonprimate animals. Indeed, there is a substantial pharmacological literature that documents the effect of neurotransmitters and neuromodulators on P3 components (Frodl-Bauch, Bottlender, & Hegerl, 1999), including various studies using noradrenergic, dopaminergic, and cholinergic agents. Unfortunately, these studies generally suffer from several limitations. Many studies are based on a limited sample size (e.g., 10 or fewer subjects), resulting in low statistical power for detecting treatment effects. Furthermore, most studies have used only one type of task: an active oddball task, meant to elicit a large P300; effects of task-irrelevant deviant stimuli were not studied. Also, almost no studies have attempted to extract separate late ERP components, despite their overlap in latency and scalp distribution. Indeed, many papers only report results from one electrode (e.g., the peak amplitude between 200 and 500 ms at electrode Pz). Finally, direct comparisons between two or more pharmacological challenges have been exceedingly rare.

Here, we report an important first step in addressing these shortcomings and toward more definitive conclusions about the neurochemical basis of late ERP responses. First, we administered an auditory oddball task with several active and passive task conditions specifically designed to elicit clear P300, novelty P3, and P3a components. Second, to deal with the issue of temporal and spatial overlap between components, we performed a rigorous temporospatial principal component analysis (PCA) of the ERP waveforms. These methods for eliciting and disentangling components of the P3 complex closely followed those used by Spencer, Dien, and colleagues (Spencer, Dien, & Donchin, 2001, Dien, 2010b, 2012). And finally, we directly compared pharmacological challenges of the noradrenergic and cholinergic system. Specifically, we administered clonidine, scopolamine, and placebo in separate sessions of a randomized crossover design. Clonidine is a centrally acting α_2 agonist that attenuates baseline noradrenergic activity by agonizing presynaptic α_2 receptors. Scopolamine is a cholinergic antagonist of the muscarinic receptors. We selected these two drugs because both have been used in several previous P3 studies (Pineda, Swick, & Foote, 1991), and because they have a comparable sedation profile.

Method

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-h 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 at rest were included in the study. All participants underwent a medical screening, which included a routine physical examination prior to being included in the experiment: only healthy individuals 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, counterbalanced double-dummy crossover design. Although both the experimenter and the participant were blind to the content of the capsule, the experimenter (SB) carried out the heart rate and blood pressure measurements, and hence received some information about the administered treatment. 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, but without clinical consequences, 60 min 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 seven participants. Clonidine, scopolamine, and placebo were administered during three separate test sessions, spaced 1 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.

Task

The auditory oddball task consisted of four conditions that were administered in four separate blocks of 300 trials each: during the first two blocks, participants were instructed to solve word puzzles (Block 1) or read either a book or a magazine, based on their preference (Block 2), while ignoring the sound stimuli (ignore blocks). During the other two (attend) blocks, participants were instructed to respond as quickly and accurately as possible to the rare stimuli with their left or right index finger (counterbalanced across participants, but kept constant within participants). The stimuli used were auditory tones of either high (500 Hz) or low pitch (350 Hz). Every tone lasted 336 ms and was presented at 70 dB(A) with an interstimulus interval of 850 ms. Tonal pitch of frequent and rare stimuli (12% of trials) was counterbalanced across participants. In all blocks, a fixation point (black plus-sign on a white background, visual angle $0.2 \times 0.2°$) was presented on the screen continuously, while auditory tones were presented. In the first three blocks, 88% of the stimuli were frequents and 12% were rares. Block 4 was comparable to Block 3, but, in addition to standard frequent (76%) and rare stimuli (12%), 36 sounds were used as infrequent novel stimuli (12%). We used six sounds each from the categories animal sounds (but not birds), birds, video game bleeps, human bodily noises, and random noises (e.g., phone, hammer). These novel sounds were the same as those used by Fabiani and Friedman (1995) and Spencer et al. (2001). Participants were not informed about the presence of novel stimuli, but they were explicitly instructed to respond to rare stimuli only.

Procedure

Participants were instructed to abstain from coffee, alcohol, and all psychoactive substances from 15 h 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 9.35 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 and scopolamine placebo), one scopolamine session (clonidine placebo and scopolamine verum), and one placebo session (clonidine and scopolamine placebos). To eliminate the confound of drug order, we 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 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 blood pressure and/or heart frequency. Furthermore, three cardio electrodes were applied to the participant's chest and connected to an electrocardiogram monitor.

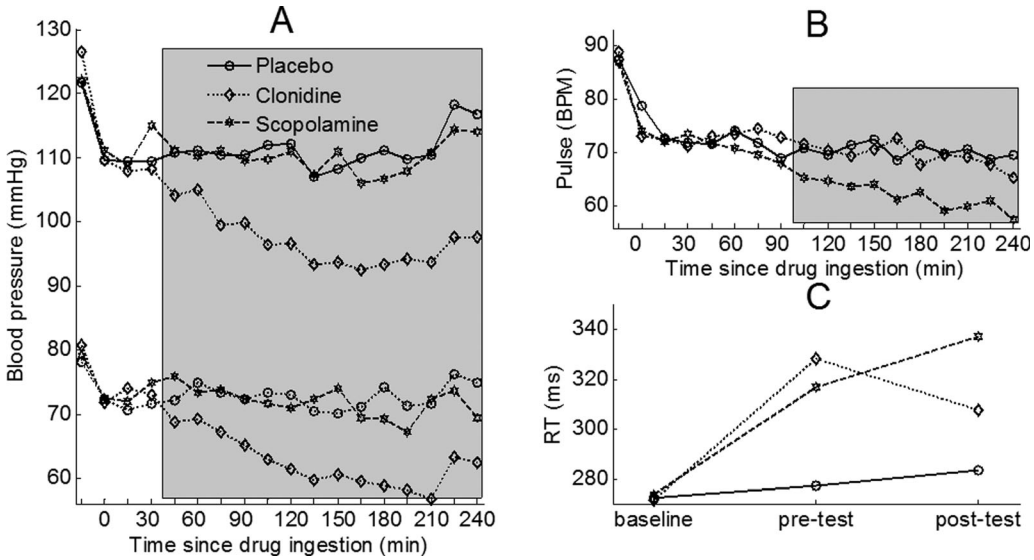

Figure 1. A: Blood pressure data for the three treatments. The shaded gray area indicates significant pairwise comparisons between clonidine and placebo ($p < .05$). B: Heart frequency for the three treatments. The shaded gray area indicates significant pairwise comparisons between scopolamine and placebo ($p < .05$). C: Results from a simple RT task, administered at the start of the test session (baseline) and right before (pretest) and after (posttest) participants performed the auditory oddball task.

Blood pressure and heart rate were then measured, and measures of participant alertness were obtained: participants completed a simple reaction time task (simple RT), in which they had to respond as quickly as possible whenever a white circle (subtending approximately 3.1° of visual angle) appeared on the black background of a computer screen. Each stimulus was presented until the response and was followed by an intertrial interval between 500–1,500 ms, varied in steps of 250 ms. To measure the sedative properties of clonidine and scopolamine, we administered the simple RT task upon a participant's arrival in the lab, as well as right before and after the participant performed the auditory oddball task.

At t = 0 min, participants ingested a microcrystalline, cellulose-filled capsule with either clonidine or placebo. Clonidine has well-established antihypertensive properties; therefore, for participant safety, blood pressure and heart rate were monitored four times an hour from t = 0 min onwards 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 = 150 min, participants performed the auditory oddball task, which lasted approximately 30 min; during the 60 min prior to this time point, participants performed two unrelated cognitive tasks (reported elsewhere). Participant fitness was checked at t = 240 min, and participants were sent home via public transportation if their blood pressure and heart rate were close to the values measured at t = −20 min. At the end of the third test session, participants received their financial compensation.

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 electrooculogram (EOG) using bipolar recordings from electrodes placed approximately 1 cm lateral to 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 preamplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of 16 times 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 cut-off of 102.4 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode producing a monopolar (nondifferential) 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 in BrainVision Analyzer 2 (Brain Products GmbH, Gilching, Germany). 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 also discarded. Data were epoched from −200 to 800 ms relative to stimulus onset and then averaged separately for each cell of the design. A 200-ms prestimulus baseline was subtracted for each ERP.

Preprocessed, segmented, averaged, and baseline-corrected data were then exported from BrainVision Analyzer and submitted to a temporospatial PCA in the ERP PCA Toolkit (Dien, 2010a). Following Spencer et al. (2001), we analyzed a 0–752 ms subwindow from the exported epochs. We first reduced ERP data dimensionality in the temporal domain, by submitting a 64 (Electrodes) × 186,624 (Observations: 384 Time Points × 9 Stimulus Types × 18 Participants × 3 Treatments) data matrix to temporal PCA. Use of a parallel test (Horn, 1965) suggested data truncation to 19 temporal factors, which were then rotated using the promax procedure (Dien, 2012). Then, to reduce the spatial dimensionality of the data, we carried out a separate spatial PCA for each of the individual spatial factors (Dien, 2010a). Use of a parallel test suggested five factors for retention; these factors were submitted to infomax rotation (Dien, 2012).

Results

Physiological and Alertness Data

Figure 1A shows that clonidine lowered systolic (mean blood pressure 101 mmHg) and diastolic (65 mmHg) blood pressure relative

Table 1. *Behavioral Results in the Classic and Novelty Oddball Blocks*

	Classic oddball				Novelty oddball			
	RT (ms)	FA	Misses	d'	RT (ms)	FA	Misses	d'
Plac	407 (50)	0.4 (0.9)	1.1 (0.5)	5.11 (0.25)	483 (76)	0.8 (1.2)	1.3 (1.6)	4.69 (0.46)
Clon	421 (49)	1.6 (0.9)	3.3 (4.5)	4.38 (0.91)	427 (92)	1.3 (1.8)	6.4 (6.8)	3.92 (0.99)
Scop	433 (81)	1.8 (2.8)	2.1 (3.7)	4.51 (0.81)	448 (79)	1.8 (1.7)	4.4 (5.9)	4.07 (1.00)

Note. Standard deviations are provided in parentheses. RT = average correct reaction time; FA = number of false alarms; Plac = placebo; Clon = clonidine; Scop = scopolamine.

to placebo (112/73 mmHg), also during performance of the oddball task (t = 150–180 min). The difference in systolic and diastolic blood pressure between placebo and scopolamine was not significant. Figure 1B shows that scopolamine (67/min) lowered heart frequency relative to placebo (72/min) and clonidine (72/min), also during (t = 150 min) and right after (t = 180 min) task performance. The difference in heart frequency between placebo and clonidine was not significant.

Results from the simple RT task (Figure 1C), administered at baseline (arrival of participant), right before, and right after performance of the oddball task, show that clonidine (303 ms) and scopolamine (309 ms) increased simple RT relative to placebo (278 ms), $F(2,34) = 5.3$, $p = .02$, $\eta_p^2 = .24$. Furthermore, mean simple RT increased as the test session progressed, $F(2,34) = 14.0$, $p < .0005$, $\eta_p^2 = .45$. The interaction between treatment and time point just reached significance, $F(4,68) = 3.2$, $p = .05$, $\eta_p^2 = .16$. Pairwise comparisons for pretest and posttest indicated that clonidine and scopolamine reliably differed from placebo, but not from each other.

Behavioral Results

Table 1 presents average RTs, accuracy, and d' values computed according to Stanislaw and Todorov (1999). In the classic oddball block, treatment did not reliably influence RT, $F(2,34) = 1.4$, $p = .26$, $\eta_p^2 = .08$. Treatment influenced perceptual sensitivity as reflected by d', $F(2,34) = 6.0$, $p = .006$, $\eta_p^2 = .26$; d' values were lower for clonidine and scopolamine than for placebo, both $ps < .005$. In the novelty oddball block, treatment reliably influenced RT, $F(2,34) = 3.7$, $p = .03$, $\eta_p^2 = .18$. Pairwise comparisons indicated that RTs for clonidine were faster than RTs for placebo, $p < .005$. However, this decrease in RTs was accompanied by decreased d', suggesting a speed-accuracy tradeoff. There was a significant main effect of treatment on d', $F(2,34) = 6.4$, $p = .004$, $\eta_p^2 = .27$, and pairwise comparisons indicated that d' was decreased relative to placebo for both clonidine and scopolamine, $ps < .005$. The decreased d' values associated with clonidine and scopolamine are consistent with our previous studies using the same treatments and participants (Brown et al., 2015).

Standard ERP Analyses

Figure 2 shows P3 scalp distributions and stimulus-locked ERP waveforms in the placebo condition. The rares in both the classic and novelty oddball blocks elicited a centroparietal P300. This impression was confirmed by a 2 (Block: classic/novelty) × 3 (Site: Fz/Cz/Pz) ANOVA on rare-locked P3 peak amplitude defined in a 200–400 ms window. This analysis indicated that the P3 peak was greater for centroparietal sites (Cz = 6.39 μV; Pz = 7.83 μV) than

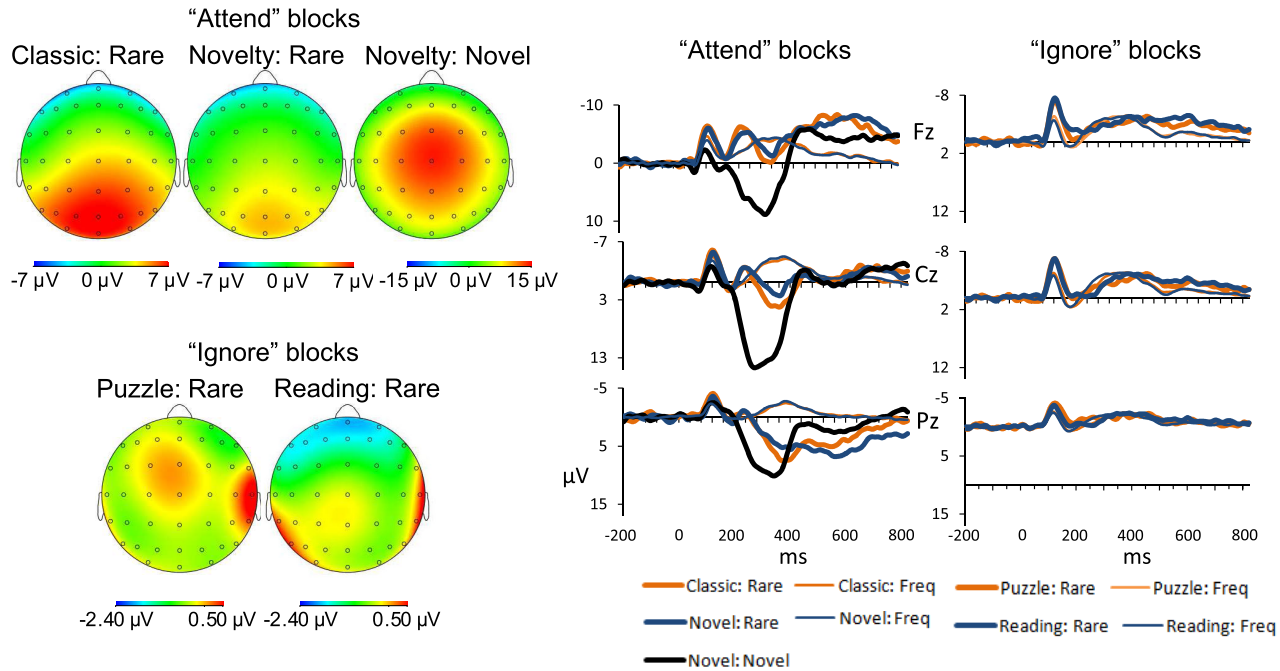

Figure 2. Scalp distributions (left) and grand-average stimulus-locked ERPs from electrodes Fz, Cz, and Pz (right) for the placebo condition. Scalp distributions reflect the time point at which the response to stimuli was most positive.

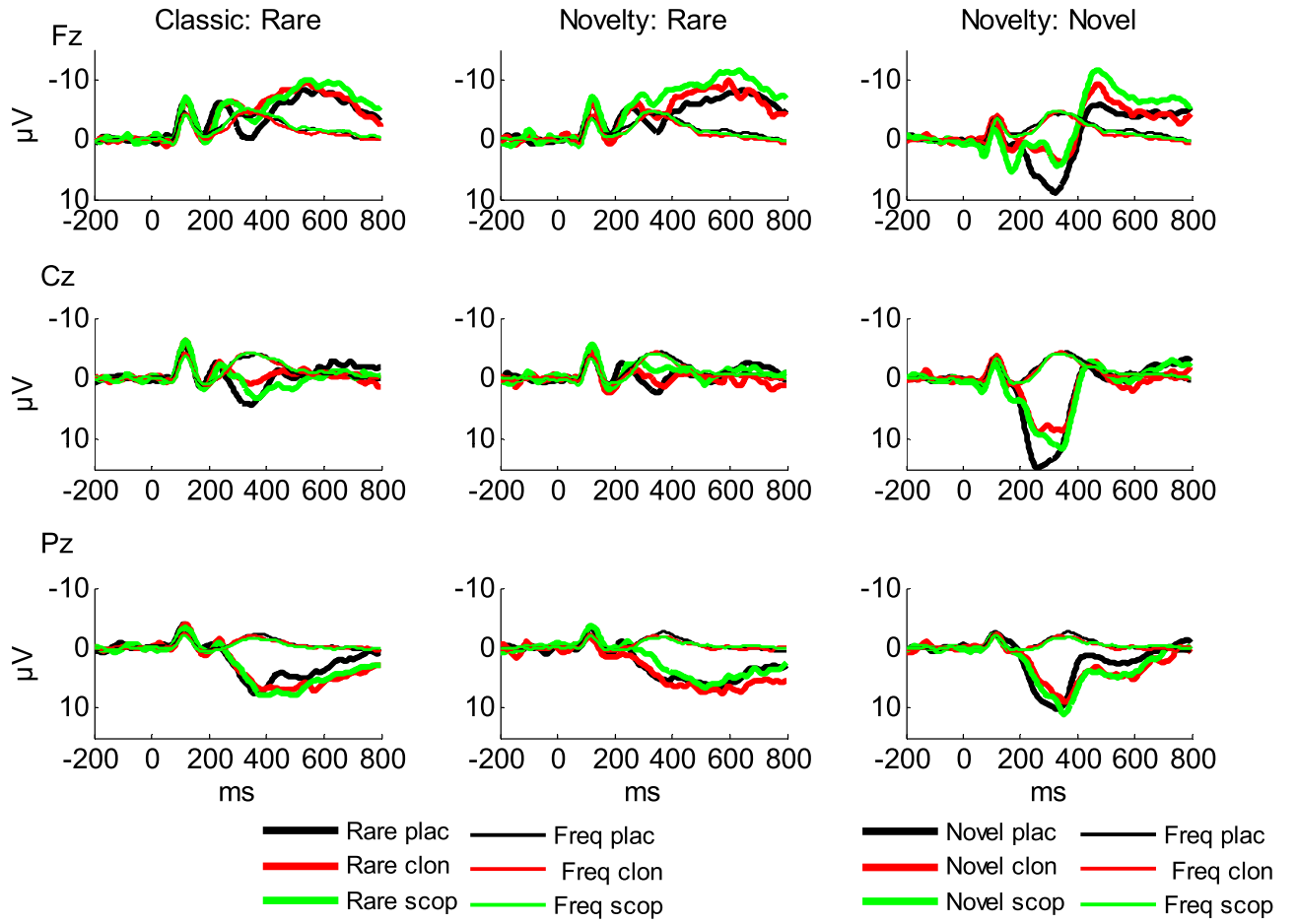

Figure 3. Grand-average stimulus-locked ERPs from the attend blocks (classic and novelty oddball) as a function of treatment.

for the frontal site Fz (2.80 μV), as indicated by a main effect of site, $F(2,34) = 22.7$, $p < .0005$, $\eta_p^2 = .57$. There was no main effect of block, nor an interaction between block and site.

As expected, novel stimuli elicited a positivity that was maximal at central electrode sites, so they shifted frontally relative to the rare-related P3. A 2 (Stimulus: rare/novel) × 3 (Site: Fz/Cz/Pz) analysis of variance (ANOVA) on stimulus-locked P3 peak amplitudes evoked in the novelty oddball block confirmed that novels evoked a different P3 scalp distribution than rares, as indicated by a significant interaction between stimulus type and site, $F(2,34) = 22.1$, $p < .0005$, $\eta_p^2 = .57$ (see Figure 2). The reliability of this interaction was confirmed with the vector-scaling procedure described in McCarthy and Wood (1985; Dien & Santuzzi, 2005). To quantify this effect, we computed difference scores as novel peak amplitude minus target peak amplitude: this revealed a larger effect at fronto-central sites (Fz = 9.3 μV, Cz = 12.6 μV) than at parietal electrode Pz (4.8 μV). Overall, P3s were larger at centroparietal sites than at frontal site Fz, $F(2,34) = 16.4$, $p < .0005$, $\eta_p^2 = .88$, and novels evoked a larger P3 than targets, $F(1,17) = 130.1$, $p < .0005$, $\eta_p^2 = .88$. Furthermore, a repeated measures ANOVA on P3 peak latency suggests that the peak latency (averaged across Fz, Cz, and Pz) is earlier for novels (277 ms) than for rares (317 ms), $F(1,17) = 6.4$, $p = .02$, $\eta_p^2 = .27$. The properties described above correspond with what is usually referred to as the novelty P3.

Taken together, the pattern of results for the attend blocks in the placebo condition is very similar to the data described in previous classic and novelty oddball studies. In the two ignore task blocks (Figure 2), it was difficult to visually identify part of the ERP as the P3a. Therefore, we did not statistically analyze the ERP data from these two task blocks.

Figure 3 presents stimulus-locked ERP waveforms elicited by rares and novels in the attend blocks as a function of treatment. Clonidine and scopolamine appeared to modulate the amplitude of the rare-related and especially novelty-related P3s. We confirmed that the drug-related modulations of the large rare-related positivity in the classic oddball block were also clearly present in response-locked averages, suggesting that they do not reflect temporal smearing of a response-related component. Having established that our data contained the expected P3 patterns in the classic and novelty oddball blocks, we subjected the ERP data to a temporospatial PCA before statistically testing for treatment effects on P3 components.

Temporospatial PCA of P3 Components

As described under Method, we first reduced temporal dimensionality of the data with a temporal PCA, which yielded 19 temporal factors, that is, 19 virtual epochs that captured the relevant temporal variance of the original data. Figure 4 shows the time courses of the first eight factors as described by the temporal factor loadings (i.e., correlations between the original time points and a given temporal factor). Based on visual inspection of these factor loadings, one temporal factor (TF2), was identified as corresponding with the P3.

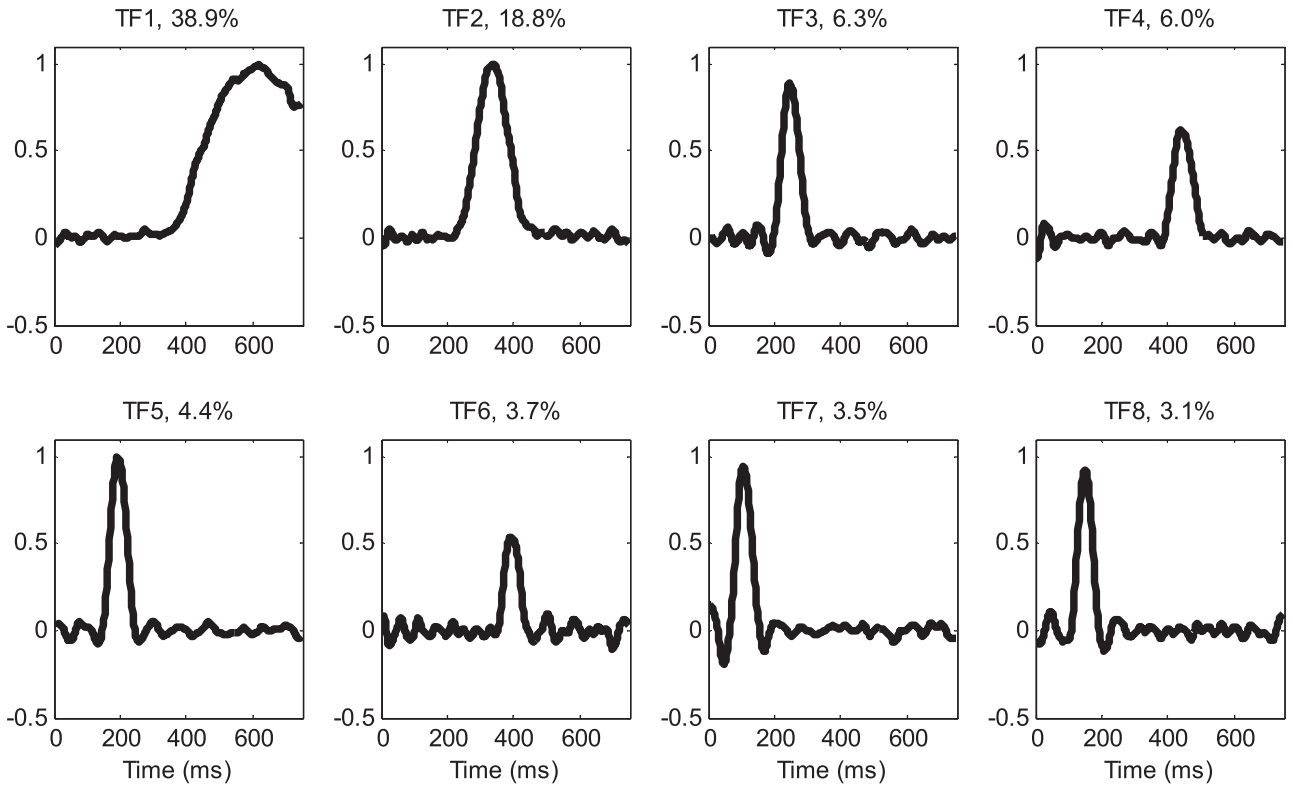

Figure 4. Temporal factor loadings, plotted as virtual epochs. Note that the values on the *Y* axis are arbitrary units, and that the sign of the factor loadings is arbitrary. For every temporal factor, the proportion of explained variance is indicated. TF2 was selected as P3 component.

The temporal PCA was followed up with a spatial PCA for TF2 to reduce the spatial dimensionality of the data. Figure 5 shows topographic maps of the spatial factor loadings associated with the first two spatial factors, TF2SF1 and TF2SF2. (The remaining spatial factors each accounted for less than 1% of the variance in the original data set.) Figure 5 also shows the contribution of these two factors to the original data, as described by the temporospatial factor scores. These factor scores are available for every cell of the design, and formed the basis for statistical analysis.

The combination of temporal factor 2 and spatial factor 1 (TF2SF1; Figure 5, top panel) appears to represent the novelty P3, given its time course (~200–400 ms) and central scalp distribution that mirrored the scalp distribution of the novelty response in the original ERP waveforms (Figure 2). Accordingly, statistical testing of the factor scores associated with TF2SF1 indicated that novels elicited a larger novelty P3 than frequents, $F(1,17) = 147.6$, $p < .0005$, $\eta_p^2 = .90$. In line with the results reported by Spencer et al. (2001), rares also elicited a significant novelty P3 in the classic oddball block, $F(1,17) = 29.1$, $p < .0005$, $\eta_p^2 = .63$, and in the novelty oddball block, $F(1,17) = 20.4$, $p < .0005$, $\eta_p^2 = .55$. Ignored rares elicited a small novelty P3 relative to ignored frequents in the puzzle block, $F(1,17) = 7.7$, $p = .01$, $\eta_p^2 = .31$, but not in the reading block, $p = .25$.

The combination of temporal factor 2 and spatial factor 2 (TF2SF2; Figure 5, lower panel) appears to represent the classic P300, given its time course (~200–400 ms) and posterior scalp distribution. In line with this interpretation, statistical testing of the factor scores associated with this temporospatial component indicated that rares elicited a larger P300 than frequents, both in the classic oddball block $F(1,17) = 21.2$, $p < .0005$, $\eta_p^2 = .56$, and in the novelty oddball block, $F(1,17) = 27.0$, $p = .0005$, $\eta_p^2 = .61$. Novel stimuli also elicited a P300, $F(1,17) = 15.5$, $p = .001$ $\eta_p^2 = .48$, but smaller than that elicited by rares, $F(1,17) = 5.1$, $p = .04$, $\eta_p^2 = .23$. A similar result was reported by Spencer et al. (2001). Rares did not elicit a significant P300 in the ignore blocks (Fs < 1).

Ignored rares have been argued to elicit both an N2 and a subsequent positivity, often called the P3a (e.g., Snyder & Hillyard, 1976; Squires, Donchin, Herning, & McCarthy, 1977), that some have argued to be distinct from the P300 and novelty P3. Our PCA did not yield a temporospatial component that was specifically elicited by ignored rares. However, as we describe above, ignored rares elicited a novelty P3 in the puzzle block, in line with the idea that the novelty P3 and P3a reflect the same component (Spencer et al., 2001).

We will now present the effects of treatment on these temporospatial factor scores. Figure 5 contains all relevant averages; to aid legibility, we have tabulated test statistics for each temporospatial component (Tables 2 and 3). In many cases, treatment effects on P3 amplitude (e.g., in the classic oddball block) were accompanied by similar effects of treatment on P3 amplitude modulation (i.e., rares > frequents). Therefore, for the sake of simplicity, when we state below that a drug modulated P3 amplitude, this generally refers to both the main effect of treatment and the interaction of treatment and stimulus type.

Relative to placebo, clonidine decreased the amplitude of the novelty P3 as evoked by both novels and classic rares (Table 2). In contrast, clonidine increased classic P300 amplitude as evoked by classic rares and, to a lesser extent, novels (Table 3). Clonidine did not affect the novelty P3 and P300 in the novelty oddball block, indicating a dissociation between rares in the two oddball blocks. Thus, clonidine decreased novelty P3 amplitude whereas, if anything, it increased P300 amplitude.

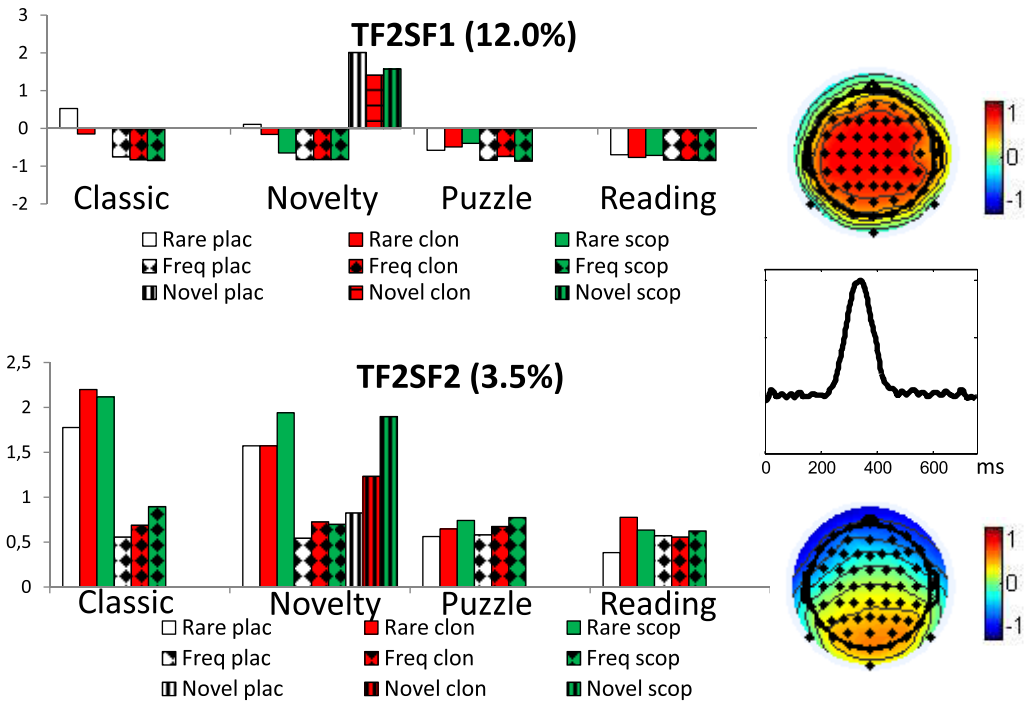

Figure 5. Temporospatial factor scores (left) and temporal and spatial factor loadings (right) associated with TF2SF1 (novelty P3) and TF2SF2 (P300), for each treatment, task, and stimulus type. The value of the factor scores is a unitless dimension. For every factor, the proportion of explained variance is indicated: note that this is the percentage of explained variance in the original set of ERPs, not in the data set that was submitted to the spatial PCA. The factor scores and spatial factor loadings of TF2SF2 were multiplied by −1 before plotting to reflect the positive polarity of the P300.

Scopolamine showed a similar pattern of results as clonidine (Figure 5; Tables 2 and 3). Relative to placebo, scopolamine decreased the amplitude of the novelty P3 evoked by classic rares, novelty rares, and novels, although the effect for novels was marginally significant. In contrast, scopolamine increased the P300 evoked by rares in the classic oddball block and by novels in the

Table 2. *TF2SF1: Statistical Effects of Treatment on Temporospatial Factor Scores*

Statistical term	F value	p value	η_p^2
Classic rare versus classic frequent			
Treatment	$F(2,34) = 6.4$	$p = .004$	.27
clo < pla	$F(1,17) = 10.5$	$p = .005$	.38
sco < pla	$F(1,17) = 5.9$	$p = .03$	.26
sco = clo		$p = .44$	.04
Treatment × Stimulus Type	$F(2,34) = 3.8$	$p = .03$	.18
clo < pla	$F(1,17) = 9.4$	$p = .007$	.36
sco ≤ pla	$F(1,17) = 3.3$	$p = .09$	.16
sco = clo		$p = .46$	.03
Novelty rare vs. novelty frequent			
Treatment	$F(2,34) = 6.4$	$p = .004$	.27
clo = pla		$p = .26$	.08
sco < pla	$F(1,17) = 15.6$	$p = .001$	.48
sco < clo	$F(1,17) = 4.8$	$p = .04$	.22
Treatment × Stimulus Type	$F(2,34) = 7.0$	$p = .003$	.29
clo = pla		$p = .15$	.12
sco < pla	$F(1,17) = 11.9$	$p = .003$	.41
sco < clo	$F(1,17) = 5.0$	$p = .04$	.23
Novelty novel versus novelty frequent			
Treatment	$F(2,34) = 4.1$	$p = .03$	.20
clo < pla	$F(1,17) = 8.6$	$p = .009$	.34
sco ≤ pla	$F(1,17) = 4.0$	$p = .06$	.19
sco = clo		$p = .48$	.03
Treatment × Stimulus Type	$F(2,34) = 3.0$	$p = .06$	.15
clo < pla	$F(1,17) = 5.4$	$p = .03$	.24
sco ≤ pla	$F(1,17) = 3.7$	$p = .07$	.18
sco = clo	$F(1,17) < 1$	$p = .57$	.02

Note. Significant main and interaction effects are followed by pairwise comparisons between the treatments. The direction of the effect is indicated. Marginally significant effects ($.05 < p < .10$) are indicated by ≤.

Table 3. *TF2SF2: Statistical Effects of Treatment on Temporospatial Factor Scores*

Statistical term	*F* value	*p* value	η_p^2
Classic rare versus classic frequent			
Treatment	$F(2,34) = 4.6$	$p = .02$	.21
clo > pla	$F(1,17) = 7.2$	$p = .02$	.30
sco > pla	$F(1,17) = 5.3$	$p = .03$	.24
sco = clo		$p = .56$	.02
Treatment × Stimulus Type		$p = .25$	.08
Novelty rare versus novelty frequent			
Treatment		$p = .42$	.05
Treatment × Stimulus Type		$p = .49$	.04
Novelty novel versus novelty frequent			
Treatment	$F(2,34) = 6.1$	$p = .006$	.23
clo ≥ pla	$F(1,17) = 4.0$	$p = .06$	.19
sco > pla	$F(1,17) = 12.3$	$p = .003$	.42
sco = clo		$p = .13$	.13
Treatment × Stimulus Type	$F(2,34) = 3.7$	$p = .04$	.18
clo = pla		$p = .39$	.05
sco > pla	$F(1,17) = 6.6$	$p = .02$	.28
sco = clo		$p = .12$	.14

Note. Significant main and interaction effects are followed by pairwise comparisons between the treatments. The direction of the effect is indicated. Marginally significant effects ($.05 < p < .10$) are indicated by ≥.

novelty oddball block. Again, no treatment effect was found for novelty rares. With one exception (see Table 2), direct comparisons between scopolamine and clonidine yielded no significant differences.

As we will discuss below, our finding in most conditions that scopolamine and clonidine increased P300 amplitude has not been reported before in the literature. To examine if a conventional analysis of the late positivity observed at Pz would have revealed these treatment effects, we computed the mean amplitude of the signal at Pz in a 200–600 ms window for rares and frequents in the classic oddball block, where the drug effects on the P300 were most pronounced. We chose a mean-amplitude measure in a relatively broad time window, because Figure 3 suggests that the drug effects were specifically evident for the trailing slope of the positivity, and hence would not be detected by a peak-amplitude analysis. However, it is worth noting that this positive deflection was probably comprised of a P300 and a positive slow wave, given that the PCA revealed a P300 factor that was more shallow. A 2 (scopolamine vs. placebo) × 2 (rares vs. frequents) repeated measures ANOVA showed a nonsignificant main effect of treatment, $F(1,17) = 1.7$, $p = .21$, and a nonsignificant interaction with stimulus type, $F(1,17) < 1$, $p = .52$. Similar results were obtained for a comparison between clonidine and placebo. Even comparisons limited to the rare-related ERPs, where differences between treatments were most evident, yielded no reliable effects of drug. We conclude that a conventional analysis would not have revealed the treatment effects on the P300 that were identified by the PCA.

Temporospatial PCA of N1 and Slow Wave Components

The physiological data and simple RT task results reported above indicate that clonidine and scopolamine caused sedation. To examine whether this affected early attention processes, we analyzed N1 amplitude, a common marker of the level of attention paid to a stimulus. The PCA analysis yielded a component, TF8SF1, that exhibited the frontocentral scalp distribution, timing, morphology, and polarity of the typical auditory N1 (Figure 6; Key, Dove, & Maguire, 2005). Statistical testing of the factor scores associated with TF8SF1 indicated that, as expected, rares elicited a larger N1 than frequents in all four task blocks, $ps < .01$ (Figure 6). Novel stimuli elicited an N1 that was smaller than that for frequents, $F(1,17) = 11.6$, $p = .003$, $\eta_p^2 = .41$, This novelty-evoked N1 was smaller for scopolamine than for placebo, $F(1,17) = 7.7$, $p = .01$, and clonidine, $F(1,17) = 5.8$, $p = .03$. Aside from this, there were no significant treatment-related main effects or interactions for any of the four blocks, indicating that the N1 evoked by rares was not sensitive to treatment. A similar pattern was observed when N1 amplitude was derived from the ERP waveforms instead of via PCA. These results suggest that clonidine and scopolamine had little or no effect on early attention.

Finally, we briefly report an analysis of the anterior-negative, posterior-positive slow wave, because previous studies have often considered the slow wave and P3 components together as part of a "late positive complex." The PCA yielded a component, TF1SF1, that given its timing, morphology, and scalp distribution may reflect the slow wave (Figure 6). Statistical testing of the factor scores associated with TF1SF1 indicated that rares elicited a larger slow wave than frequents in all four task blocks, $ps < .005$, and that novel stimuli also elicited a slow wave, $F(1,17) = 33.1$, $p < .0005$, but smaller than that elicited by rares, $F(1,17) = 8.7$, $p = .009$. There were no significant treatment-related main effects or interactions in the classic oddball block and in the two ignore blocks. In the novelty oddball block, clonidine did not affect TF1SF1, but scopolamine led to an increased rare-evoked slow wave amplitude modulation (i.e., interaction with stimulus type) compared to placebo, $F(1,17) = 5.3$, $p = .03$, and clonidine, $F(1,17) = 4.5$, $p = .048$; and to increased slow wave amplitude (i.e., main effect) and amplitude modulations compared to clonidine, both $Fs = 9.8$, $ps = .006$, but not placebo.

Discussion

To examine the neurochemical basis of late ERP responses to deviant stimuli, we collected EEG data while participants performed an auditory oddball task with several active and passive task conditions. We then used temporospatial PCA to extract two distinct late positive ERP components: the P300, which was elicited by attended rares and, to a lesser extent, by novels; and the novelty

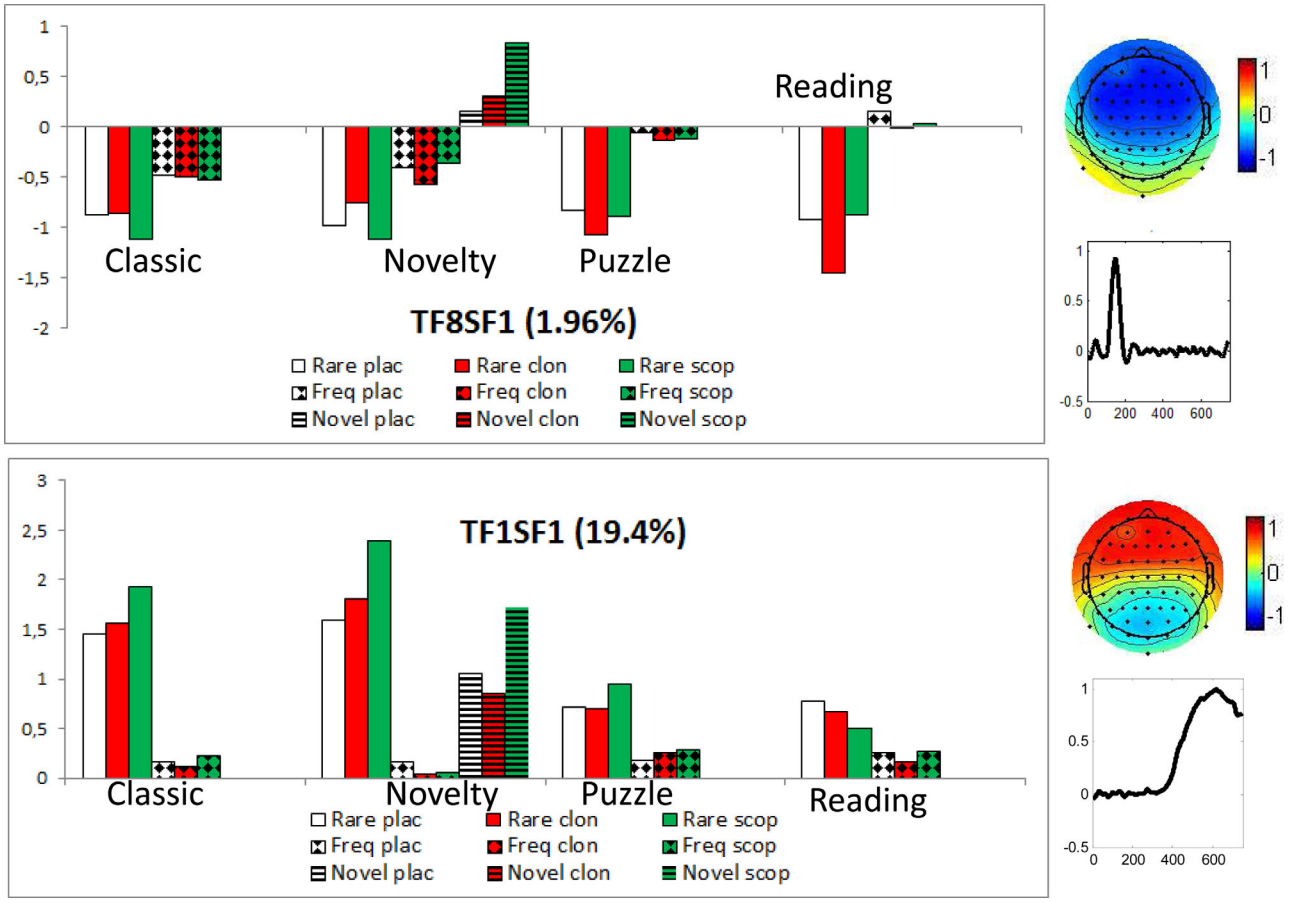

Figure 6. Temporospatial factor scores (left) and temporal and spatial factor loadings (right) associated with TF8SF1 (N1) and TF1SF1 (slow wave), for each treatment, task, and stimulus type. The value of the factor scores is a unitless dimension. For every factor, the proportion of explained variance is indicated: note that this is the percentage of explained variance in the original set of ERPs, not in the data set that was submitted to the spatial PCA.

P3, which was elicited by novels but also by attended rares. In line with several previous PCA studies, we failed to find evidence for a distinction between the novelty P3 and P3a, suggesting instead that they reflect the same component (Dien, Spencer, & Donchin, 2004; Simons, Graham, Miles, & Chen, 2001; Spencer et al., 2001). Together, these results replicate the key findings of Spencer et al. (2001), whose methods formed the basis for our study.

Our specific goal was to examine how the P300 and novelty P3 components were modulated by clonidine and scopolamine. Clonidine, at the moderate dose used here, reduces activity in the noradrenergic nucleus locus coeruleus and decreases norepinephrine release in projection areas throughout the brain. The effects of scopolamine are somewhat more complicated (Hasselmo & Sarter, 2011). Scopolamine blocks postsynaptic muscarinic receptors, but also presynaptic muscarinic autoreceptors in cholinergic basal forebrain neurons, which increases overall acetylcholine release. This, in turn, leads to increased stimulation of nicotinergic acetylcholine receptors, which, like muscarinic receptors, are widely distributed across the brain. Despite these fundamental differences in their principal modes of action, clonidine and scopolamine had surprisingly similar effects on the examined P3 components. We will now examine the drug effects in turn, first focusing on the P300 and then on the novelty P3.

Scopolamine and clonidine increased the amplitude of the P300 to rares in the classic oddball block and to novels. Neither drug modulated the P300 to rares in the novelty oddball block. The different treatment effects for the attended rares in the two active oddball blocks were also clearly apparent in the ERP waveforms (Figure 3) and the behavioral results (Table 1), suggesting that the addition of infrequent novel stimuli changed task processing in a way that interacted with the obtained treatment. Previous studies of the effects of scopolamine and clonidine on the P300 all used active oddball tasks or other discrimination tasks for eliciting the P300. No previous studies have reported that scopolamine enhances the P300, although it should be emphasized that previous studies have usually reported results for only a few electrodes and have not attempted to decompose the ERP data (e.g., Curran, Poovi-boonsuk, Dalton, & Lader, 1998; Meador et al., 1989). Several studies reported no significant effect of scopolamine on the amplitude of the late positive ERP response at Pz (Callaway, Halliday, Naylor, & Schlechter, 1985; Potter, Pickles, Roberts, & Rugg, 2000a, 2002b). One study reported an amplitude reduction at Pz (Brandeis, Naylor, Halliday, Callaway, & Yano, 1992), and a final study reported an amplitude reduction by scopolamine and no interaction with electrode site (Fz, Cz, Pz; Curran et al., 1998). We do not know why our pattern of results diverges somewhat from previous literature. The scopolamine-induced amplitude increase for attended rares was evident primarily for the trailing tail of the late positivity (which presumably consisted of a P300 and positive slow wave), not for the peak, and we found that a conventional mean-

amplitude analysis of the Pz data would not have detected this treatment effect. However, in those previous articles that plotted the Pz waveforms, we noticed no hint of a scopolamine-induced amplitude increase of the trailing tail.

Previous work is also generally at odds with our findings that clonidine, if anything, increased the P300. Two studies found no reliable effect of clonidine on the amplitude of the late positive response over posterior electrodes (Shelley et al., 1997; Turetsky & Fein, 2002). Three other studies found a reliable amplitude reduction after clonidine (Duncan & Kaye, 1987; Halliday et al., 1994; Joseph & Sitaram, 1989). Most studies used a dose similar to that used here. In general, we have noticed no systematic relationship between scopolamine and clonidine dose in previous studies and whether or not the results matched ours. Altogether, the general discrepancy between our P300 findings and those in previous scopolamine and clonidine studies is puzzling. Some of the discrepancy may be due to the small sample sizes used in previous research in combination with the possibility that individuals may show highly diverse, or even opposite, effects of the same pharmacological agent on P300 amplitude, depending on tonic neuromodulator levels or personality traits (de Rover et al., 2015). In any case, the discrepancy emphasizes the need for more solid research, using PCA or other decomposition methods to isolate the P300 (Dien, 2012).

Whereas scopolamine and clonidine tended to increase the posterior P300, they decreased, in most conditions, the amplitude of the more frontally distributed novelty P3. To our knowledge, there have been no previous studies that examined the effects of scopolamine or clonidine on the late frontal response to novel stimuli, the stimulus class that probably elicits the most pronounced novelty P3. However, some information may be gleaned from reported drug effects on the late frontal response to attended rares. Here, previous literature is more consistent with our findings. Two scopolamine studies reported a reduced P3 amplitude at Fz (Potter, Pickles, Roberts, & Rugg, 2000b) and Cz (Meador et al., 1989). One clonidine study reported a reduced frontal P3 (Turetsky & Fein, 2002), while another study reported no effect of clonidine over frontal electrodes (Joseph & Sitaram, 1989). Together these results present fairly strong evidence that scopolamine and clonidine decrease the amplitude of the novelty P3. A possibly related finding is that clonidine reduces the amplitude of the stop P3 (Logemann, Böcker, Deschamps, Kemner, & Kenemans, 2013), a frontocentral component associated with successful inhibitions, which requires a systematic comparison with other frontal P3 components.

Why did clonidine and scopolamine show such similar effects on the late positive components? A plausible reason is that the central noradrenergic and cholinergic systems strongly interact with each other. On the one hand, there is solid evidence that stimulation of the locus coeruleus inhibits cortical acetylcholine release (Acquas, Wilson, & Fibiger, 1998; Bianchi, Spidalieri, Guandalini, Tanganelli, & Beani, 1979), probably through the activation of presynaptic α_2 receptors in the basal forebrain and on cortical cholinergic nerve endings (Beani, Bianchi, Giacomelli, & Tamberi, 1978; Buccafusco, 1982). In addition, there is some in vitro evidence that clonidine may also directly block muscarinic receptors (Buccafusco & Aronstam, 1986). On the other hand, acetylcholine has been demonstrated to activate locus coeruleus neurons in rats, and coadministration of scopolamine reduces this effect (Adams & Foote, 1988; Egan & North, 1985; Engberg & Svensson, 1980), suggesting that the effect of acetylcholine on locus coeruleus neurons is mediated by muscarinic receptors. So the locus coeruleus and basal forebrain strongly interact with each other, and clonidine and scopolamine may each have reduced this interaction, leading to a similar pattern of results for the two drugs. This view is further supported by findings that lesions to both the locus coeruleus (Pineda, Foote, & Neville, 1989) and to the nucleus basalis of Meynert (Wang et al., 1997), the primary source of cortical acetylcholine, result in a significant amplitude reduction of the late positivity to rares in a passive auditory oddball task.

One might argue that the similar results obtained with clonidine and scopolamine are mediated by their comparable sedation profiles rather than by their pharmacological mechanisms of action and interaction. However, we believe that the pharmacological (neurobiological) effects of the two drugs and their subjective (psychological) sedation effects represent two levels of description of the same phenomenon, rather than competing accounts of our findings. That is, the broadly projecting (descending and ascending) neuromodulatory arousal systems that have the unique properties for causing (or modulating) a brainwide phenomenon such as the P3, are the same systems that make such important contributions to our general state of arousal (and hence subjective level of sedation; Berridge, 2008; Robbins, 1997). At the same time, it is possible that the sedation caused by the two drugs affected early attention to the stimuli, and that the drug effects on P3 components are an indirect effect of this decrease in attention rather than a direct effect of the drugs on the systems that generate the P3 components. Although we cannot fully exclude this possibility, our finding that clonidine and scopolamine did not affect the amplitude of the rare-evoked N1 in any of the four task blocks strongly suggests that the drug-related sedation was not accompanied by a reduction in attention.

A question for future research is why clonidine and scopolamine have differential or even opposite effects on the amplitudes of the posterior P300 and frontal P3 components. An interesting possibility is that this pattern reflects the important role of norepinephrine and acetylcholine in modulating the balance between ("bottom-up") thalamocortical input and ("top-down") intracortical activity (Hasselmo & Sarter, 2011; Yu & Dayan, 2005). However, in light of the complicated effects of clonidine and scopolamine, interactions between the neuromodulator systems, and the fact that very little is known about the cellular basis of P3 components (cf. Nieuwenhuis et al., 2005), this hypothesis remains purely speculative. One way to address the hypothesis in humans would be to examine the effects of clonidine and scopolamine on functional connectivity patterns in EEG and neuroimaging data (Coull, Büchel, Friston, & Frith, 1999), and relate these to drug effects on P3 components.

To summarize, the present results complement previous findings (de Rover et al., 2015; de Taeye et al., 2014; Nieuwenhuis, 2011; Nieuwenhuis et al., 2005) in suggesting an important role of the noradrenergic system in the generation of the frontal novelty P3 and the posterior P300, although the drug-related increase in P300 amplitude observed here appears at odds with the drug-related decrease in P300 amplitude observed in several previous studies. In addition, the results provide unequivocal evidence for a role of the cholinergic system in generation of not only the novelty P3 (Ranganath & Rainer, 2003), but also the posterior P300. Future research in animals, for example, using optogenetic methods, needs to examine the role of interactions between the two neuromodulator systems in generating P3 components.

Another goal for future research will be to test the hypothesis that dopamine is involved in generating the P3a/novelty P3 (Polich, 2007). While specific dopaminergic agents have little or no effect

on the late positive response to attended rares (Luthringer et al., 1999; Oranje et al., 2006; Takeshita & Ogura, 1994), there is some evidence that they affect the late positive response to ignored rares and novel stimuli (Kähkönen et al., 2002; Rangel-Gomez, Hickey, van Amelsvoort, Bet, & Meeter, 2013). However, these effects were observed at centroparietal rather than frontal electrodes, and no attempt was made to distinguish specific components contributing to the late positive response. Therefore, methods such as those used here are needed to examine the relationship between dopamine and P3 components.

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