

Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission



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Abstract

In this double-blind, placebo-controlled study, we examined the effects of subanaesthetic doses of ketamine (an NMDA glutamate receptor antagonist) and thiopental (a GABA-A receptor agonist) on the event-related potential (ERP) correlates of deviant stimulus processing in 24 healthy adults. Participants completed three separate pharmacological challenge sessions (ketamine, thiopental, saline) in a counter-balanced order. EEG data were recorded both before and during each challenge while participants performed a visual 'oddball' task consisting of infrequent 'target' and 'novel' stimuli intermixed with frequent 'standard' stimuli. We examined drug effects on the amplitude and latency of the P300 (P3) component of the ERP elicited by target (P3b) and novel stimuli (P3a), as well as the N200 (N2) component elicited by both target and novel stimuli, and the N100 (N1) elicited by standard stimuli. Relative to placebo, both drugs reduced the amplitude of parietal P3b. While both drugs reduced parietal P3a and Novelty N2, ketamine also shortened P3a latency, reduced Novelty N2 amplitude more than thiopental, and increased frontal P3a amplitude relative to placebo. Overall, the data suggest that both the GABA-A and NMDA receptor systems modulate P3b and P3a. NMDA antagonism appears to lead to more varied effects on the neural correlates of novelty processing.

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Introduction

Glutamate and gamma-aminobutyric acid (GABA) are the primary excitatory and inhibitory neurotransmitters in the brain and are probably involved in most aspects of cognition. Dysregulation of these systems is thought to play a role in the pathophysiology of a number of disorders, including alcoholism (Krystal

et al., 2003b,c, 2006; Petrakis et al., 2004). The P300 (P3) component of the event-related potential (ERP) is generated by distributed cortical sources involved in processing contextually deviant stimuli, an integral component in a variety of cognitive operations. P3 alterations may be endophenotypic markers of the genetic risk of alcoholism and other disorders (Polich and Criado, 2006; Porjesz et al., 2005).

In this double-blind, placebo-controlled, pharmacological challenge study, we examined the role of *N*-methyl-*D*-aspartate (NMDA) glutamate and GABA-A receptor function in modulating the P3 component in healthy adults. To our knowledge, this is the first study to administer a GABA-A agonist (the barbiturate, thiopental), a non-competitive NMDA antagonist (ketamine), and placebo in a within-subjects design to

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Portions of this study were initially presented at the 2007 Annual Meeting of the Research Society of Alcoholism (Chicago, IL), and the 2007 Annual Meeting of the American College of Neuropsychopharmacology (Boca Raton, FL).

study the effects of these systems on the P3. These data were collected as part of a larger, ongoing study examining the effects of ketamine and thioipental in healthy individuals with and without a family history of alcoholism. Thus, in addition to the primary goal of expanding our basic understanding of the neuropharmacology of P3 in healthy adults, these data were collected to validate the use of ERPs (in particular, P3) as objective, non-invasive markers of neurocognitive function in future pharmacological challenge studies.

The P3 component has been extensively studied in a variety of contexts (for recent reviews, see Polich and Criado, 2006; Polich, 2007). It is frequently elicited using variations of the 'oddball' paradigm in which participants detect infrequent 'target' stimuli, and in some cases infrequent non-target stimuli, interspersed among frequent 'standard' stimuli. P3 represents a family of related but dissociable components (Courchesne et al., 1975; Squires et al., 1975) including the 'Target' P3b (elicited by infrequent, task-relevant target stimuli) and the 'Novelty' P3a (elicited by infrequent, task-irrelevant non-target stimuli). P3b is frequently associated with context updating and allocation of attentional resources (see Polich, 2007), and is generated by multiple cortical sources, including the temporo-parietal junction, frontal cortex, and parietal association areas (Bledowski et al., 2004; Halgren et al., 1998; Knight, 1984, 1996; Polich and Criado, 2006; Soltani and Knight, 2000). P3a probably represents an automatic orienting response to novel or otherwise salient stimuli (Courchesne et al., 1975; Knight, 1984) mediated by an interaction between prefrontal, temporal, and parietal cortical sources (Bledowski et al., 2004; Halgren et al., 1998; Knight, 1984, 1996; Polich and Criado, 2006; Soltani and Knight, 2000).

It is probable that the neuropharmacologies of P3a and P3b are at least partially dissociable (see Polich and Criado, 2006). For example, recent evidence demonstrates the importance of the locus coeruleus–norepinephrine system in generating P3b (Nieuwenhuis et al., 2005), while frontal dopaminergic pathways are important in generating P3a (see Polich, 2007; Polich and Criado, 2006). Although neuromodulators such as norepinephrine and dopamine are clearly important in generating P3a/b, the basic neurotransmitters such as GABA and glutamate are also likely to be involved (Frodl-Bauch et al., 1999). The latter are of particular interest because the underlying neuro-oscillatory activity that comprises ERPs like the P3 may depend on the interplay between excitatory NMDA and inhibitory GABAergic receptors (Ford et al., 2007).

Comparatively few studies have used selective pharmacological challenges to examine the influences

of NMDA and GABA activity on P3. However, at least two groups have reported that ketamine attenuates auditory (Oranje et al., 2000) and visual P3b amplitude (Ahn et al., 2003). Several groups have also found that benzodiazapines attenuate auditory P3b amplitude (Hayakawa et al., 1999; Reinsel et al., 1991; Rockstroh et al., 1991), and one previous report (Fowler and Mitchell, 1997) found a barbiturate to affect the latency (but not amplitude) of the visual P3b.

In contrast to these prior challenge studies, we examined the effects of ketamine and thioipental on *both* the P3b and P3a components elicited during a visual oddball paradigm. Thus, this is one of the first reports to explore the effects of these drugs on P3a and other ERP correlates of novelty processing. Due to factors such as practice effects and test–retest habituation, we expected to observe attenuation of P3a/b amplitude from pre- to post-infusion on placebo day. However, we predicted that both thioipental and ketamine would lead to greater attenuations of P3a/b amplitude. We also predicted that both ketamine and thioipental would alter P3a/b latency. In addition, we explored whether the effects of these drugs on P3a/b were related to their behavioural performance effects. Finally, we examined the effects of the drugs on the N200 (N2) component elicited by target and novel stimuli, and on the N100 (N1) component elicited by standard stimuli. Thus, we not only examined the effects of ketamine and thioipental on the neural correlates of target and novelty processing, but also on the neural correlates of basic sensory processing.

Methods

This protocol was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System (West Haven, CT, USA) and the Human Investigations Committee of the Yale University School of Medicine (New Haven, CT, USA). Participants' safety was reviewed on an ongoing basis by the Data Safety Monitoring Board of the NIAAA Center for the Translational Neuroscience of Alcoholism. All participants gave written informed consent prior to the onset of the study.

Participants

Twenty-four healthy adults were recruited by public advertisement. One was excluded from analysis due to excessive EEG artifacts, leaving a sample of 23 [eight female; age (mean \pm s.d.) = 24.55 \pm 2.59 yr]. Five of the participants had a family history of alcoholism, a distinction that is the focus of a larger study for which

data collection is ongoing, but is not addressed in the present study.

All participants were medically and neurologically normal (based on history, physical examination, EKG, and screening laboratories), and underwent psychiatric screening using the Structured Clinical Interview for DSM-IV (First et al., 2002). Participants had previously used alcohol but had no history of alcohol abuse or dependence, other Axis I psychopathologies, or a family history of psychosis. Participants remained alcohol-free for 3 d prior to the first test day and for the duration of the testing period, and completed urine toxicology and alcohol breathalyser tests on each test day. Participants fasted the night before and for the duration of each session to minimize the risk of nausea.

Drug challenge parameters

Three separate, double-blind, drug challenge sessions were conducted with at least a 3-d interval between sessions. Each session consisted of a 60-min intravenous infusion of saline (placebo), ketamine (0.23 mg/kg loading and infusion rate 0.58 mg/kg.h), or thiopental (1.5 mg/kg loading and infusion rate of 40 μ g/kg.min), and was supervised by an anaesthesiologist (A.P.). Doses were selected to have mild-to-moderate psychogenic and sedating effects based on previous studies (Krystal et al., 1994, 2005a,b) and were well tolerated. The order of sessions was counter-balanced across participants. ERP data were collected as part of a larger study comparing the psychiatric and behavioural effects of ketamine and thiopental. To assess subjective arousal and intoxication, ratings from visual analogue scales (VAS) were obtained at multiple time-points. Analyses from this larger sample revealed that the two drugs did not lead to significantly different levels of sedation, although ketamine had greater euphoric effects than thiopental (Dickerson et al., unpublished observations).

Experimental paradigm and procedure

Participants were seated in a dimly lit, sound-attenuated, testing booth and completed two runs of a three-stimulus visual oddball task approximately 90 min before and 45 min after the initiation of infusion. The task consisted of standard (small blue circle, white background, 80%), target (large blue circle, white background, 10%), and novel (non-repeating fractal images, 10%) stimuli presented in pseudo-random order on a computer display. Stimuli were presented for 500 ms with an inter-stimulus interval of 1500 ms. Each run consisted of three blocks of

150 stimuli. Participants were instructed to respond only to the target stimulus by pressing a button using their right hand.

EEG recording and analysis parameters

EEG data were acquired using sintered electrodes from three midline scalp sites (Fz, Cz, Pz) using a linked-earlobe reference and a fronto-central ground. The electro-oculogram was recorded horizontally (HEOG) from electrodes placed at the outer canthi of the eyes and vertically (VEOG) from electrodes placed above and below the right orbit. The data were digitized at 1000 Hz with a gain of 500, and were bandpass filtered between 0.1 and 100 Hz during acquisition. Electrode impedances did not exceed 10 k Ω . Data were low-pass filtered at 30 Hz offline prior to epoching.

ERP epochs were obtained from -100 ms to 1000 ms following stimulus presentation. An automated ocular correction routine (Gratton et al., 1983) was applied to remove blink and eye-movement artifacts. Epochs were baseline-corrected using a -100 ms to 0 ms interval. Any corrected epochs containing EEG amplitudes exceeding ± 75 μ V were excluded from analysis. Error trials were also excluded. ERP averages were created for each stimulus type (standard, target, novel) \times drug type (placebo, ketamine, thiopental) \times time (pre- and post-infusion) combination.

Based on inspection of the grand-average waveforms, the P3b component was defined as the largest positive-going peak (point of peak amplitude relative to the pre-stimulus baseline) in a latency window of 300–500 ms following target stimulus onset. The P3a component was defined as the largest peak in a latency window of 250–450 ms following novel stimulus onset. The N2 component was defined as the negative-going peak immediately preceding the P3a/b component. The N1 component was defined as the largest negative-going peak in a latency window of 130–200 ms following standard stimuli. An automated computerized routine was used to measure the peak amplitudes of the P3a/b and N1 components and the peak latencies of the P3a/b components. A semi-automatic, computerized routine was used to measure the peak amplitude of the N2 component. Peak detections were performed on each individual participant's grand-average waveform for each time and condition.

Oddball behavioural data

Behavioural performance measures included the number of omission errors to target stimuli (misses), the number of commission errors to novel and standard stimuli (false alarms), and the mean response time

Table 1. Oddball paradigm behavioural results

Stimulus	Variable	Drug type	Pre-infusion	Post-infusion	Primary effects
Target	RT	Placebo	408 (17)	414 (15)	Drug \times time interaction ($p < 0.01$) relative to placebo, both ketamine ($p = 0.03$) and thiopental $p < 0.01$) delay response time
		Ketamine	417 (19)	460 (20)	
		Thiopental	422 (18)	491 (22)	
	Errors	Placebo	0.7 (0.3)	2.1 (0.9)	n.s.
		Ketamine	1.0 (0.4)	2.0 (0.5)	
		Thiopental	1.5 (0.6)	4.0 (1.4)	
Novel	Errors	Placebo	0.2 (0.1)	0.3 (0.2)	n.s.
		Ketamine	0.4 (0.2)	0.1 (0.1)	
		Thiopental	0.3 (0.1)	0.1 (0.1)	
Standard	Errors	Placebo	0.3 (0.1)	0.4 (0.2)	Trend level main effect for drug type
		Ketamine	0.6 (0.2)	0.7 (0.2)	
		Thiopental	0.9 (0.3)	0.8 (0.2)	

Values are mean (S.E.).

(RT) to targets. One participant's behavioural data for the placebo day were unavailable due to computer error.

VAS euphoria ratings as potential covariates

Analysis of the larger sample from the behavioural study (Dickerson et al., unpublished observations) revealed ketamine had greater euphoric effects than thiopental. Accordingly, we examined VAS scores measuring subjective intoxication ('high' and 'buzzed') as potential covariates for ERP analyses. To capture the overall euphoria levels during the infusion period, we averaged the 15- and 45-min post-infusion scores of each item. One participant's 45-min post-infusion VAS ratings for the thiopental session were unavailable. The ketamine-induced euphoria scores did not significantly correlate with changes in P3a or P3b amplitudes from pre- to post-infusion. Accordingly, these VAS variables were not included as covariates in the ERP analyses.

Statistical analysis plan

ERP and behavioural data were analysed using repeated-measures analyses of variance (ANOVA). Behavioural data were analysed using a drug type \times time design, while ERP data were analysed using a drug type \times electrode \times time design. An α of 0.05 was used for all analyses. Greenhouse–Geisser corrections for non-sphericity were used for all comparisons with more than two levels. Effect sizes are reported as partial η^2 values.

Our primary interest was in assessing ERP and behavioural changes from pre- to post-infusion runs

within a drug challenge session. The magnitude of these changes was expected to differ between drugs and across electrodes. Accordingly, simple interaction contrasts (Keppel, 1991) were employed to isolate the simple effects of significant higher-order interactions in all ERP and behavioural analyses. For each significant drug type \times electrode \times time interaction, we tested the interaction of each pairwise combination of drug type and time separately for each electrode.

Correlational analyses

Pearson product-moment correlation coefficients ($\alpha = 0.05$, two-tailed) were used to examine the relationship between changes in P3a/b amplitude following drug administration (post-infusion minus pre-infusion) and changes in target RT following drug administration (post-infusion minus pre-infusion). In addition, correlation coefficients were used to describe the relationship between the changes in the different ERP components following drug administration. In particular, we were interested to see if changes in early sensory processing (indexed by N1 to standard stimuli) were related to changes in later, cognitive processing (indexed by N2 and P3 to target and novel stimuli).

Results

Behavioural data

Table 1 displays pre- and post-infusion oddball performance data. A significant drug type \times time interaction was found for target RT [$F(2, 42) = 6.37$, $p < 0.01$, $\eta_p^2 = 0.23$]. Post-infusion RT was significantly delayed

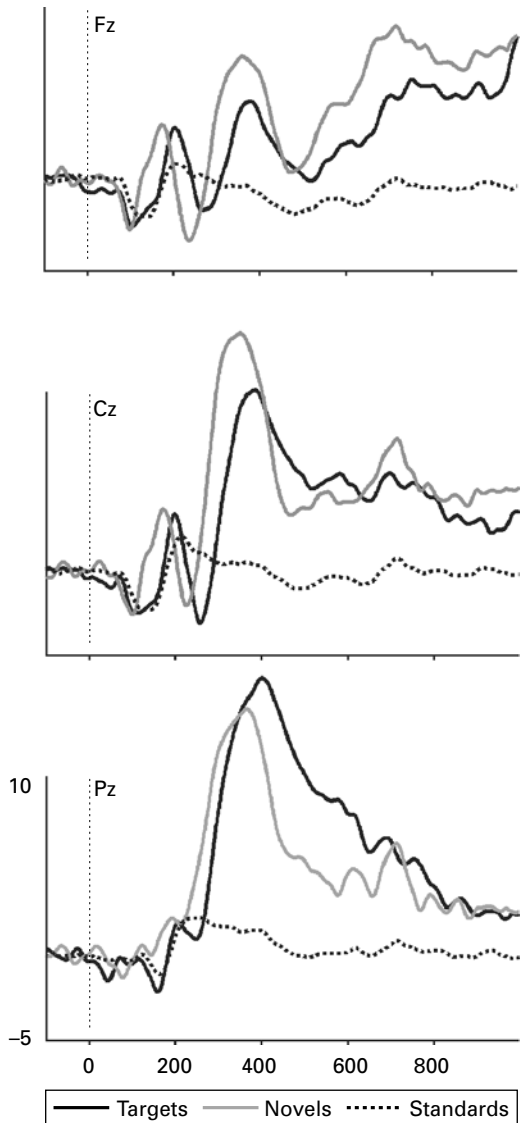


Figure 1. Grand-average ERP waveforms elicited by target, novel, and standard stimuli during the pre-infusion placebo run at Fz, Cz, and Pz.

for both ketamine and thiopental sessions ($p=0.001$ in both cases). Interaction contrasts revealed the magnitude of RT delay was significantly greater for thiopental [$F(1, 21)=8.73$, $p<0.01$, $\eta_p^2=0.29$] and ketamine [$F(1, 21)=5.63$, $p=0.03$, $\eta_p^2=0.21$] than placebo. RT delays tended to be larger for thiopental than ketamine ($p=0.07$, $\eta_p^2=0.14$). No significant effects of drug type or drug type \times time interactions were found for either omission errors to target stimuli or false-alarm errors to novel stimuli. A trend level ($p=0.06$, $\eta_p^2=0.13$) main effect for drug type was found on errors to standard stimuli. There were more errors in thiopental than placebo sessions. However, this effect did not

interact with time, nor were there any significant differences between thiopental and ketamine.

ERP data

Target stimuli generated typical P3b components with parietal maxima, while novel stimuli generated P3a components with a more fronto-central distribution (Figure 1). Figures 2 and 3 display the pre- and post-infusion grand-average ERPs elicited by target and novel stimuli on each test day, while Figure 4 displays ERPs elicited by standard stimuli. Table 2 displays pre- and post-infusion amplitudes for all measured components, peak latencies for the P3a/b components, and a summary of the primary significant effects. Table 3 lists other significant effects found in the overall ANOVAs.

ERPs to target stimuli

P3b amplitude

The primary finding was a significant drug type \times electrode \times time interaction effect [$F(4, 88)=2.65$, $p=0.05$, $\eta_p^2=0.11$]. Baseline amplitude differences between conditions were not significant at any electrode site. Significant differences in pre- and post-infusion P3b amplitude were found at electrodes Cz and Pz for all three conditions ($p\leq 0.05$ in each case). However, significant differences in the magnitude of P3b attenuations were also found between placebo and the active drugs. The results of pairwise interaction contrasts are as follows:

Ketamine vs. placebo. There was a significant drug type \times electrode \times time interaction [$F(2, 44)=3.48$, $p=0.04$, $\eta_p^2=0.14$]. Relative to placebo, ketamine significantly attenuated P3b amplitude at electrode Pz [$F(1, 22)=6.73$, $p=0.02$, $\eta_p^2=0.23$].

Thiopental vs. placebo. There was a significant drug type \times electrode \times time interaction [$F(2, 44)=4.88$, $p=0.02$, $\eta_p^2=0.18$]. Relative to placebo, thiopental significantly attenuated P3b amplitude at electrode Pz [$F(1, 22)=13.98$, $p=0.001$, $\eta_p^2=0.39$] and at the trend level at Cz ($p=0.07$).

Ketamine vs. thiopental. No significant differences were found between the effects of ketamine and thiopental on P3b amplitude.

P3b latency

There were no significant effects of drug type, time, or their interaction, on target P3b latency.

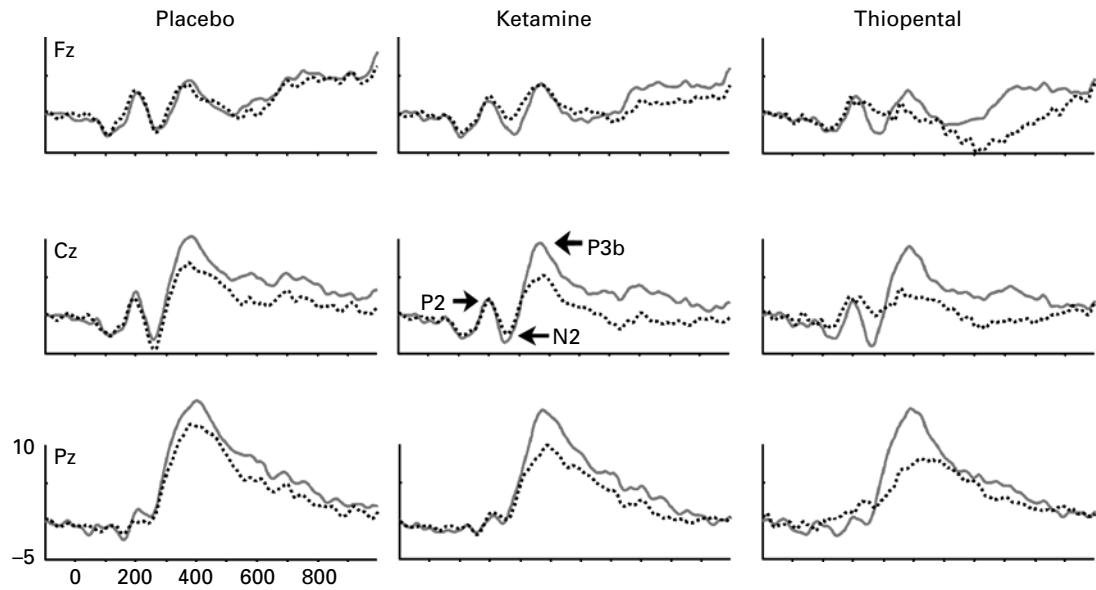


Figure 2. Pre-infusion (—) and post-infusion (·····) grand-average ERP waveforms elicited by target stimuli at Fz, Cz, and Pz.

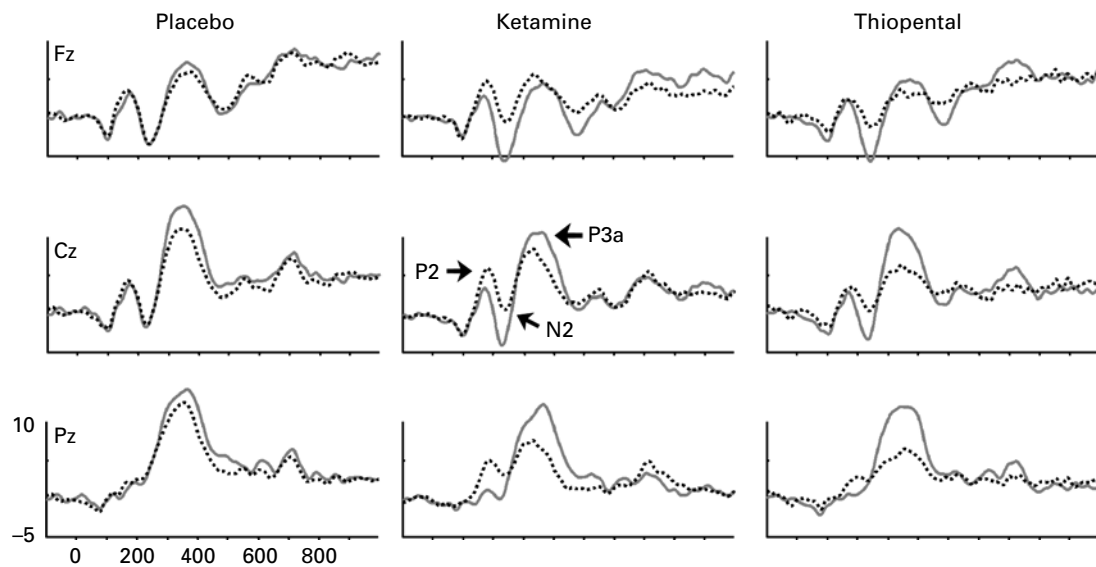


Figure 3. Pre-infusion (—) and post-infusion (·····) grand-average ERP waveforms elicited by novel stimuli at Fz, Cz, and Pz.

N2 amplitude

There was a significant drug type \times time interaction effect [$F(2, 44) = 4.39$, $p = 0.02$, $\eta_p^2 = 0.17$]. Interaction contrasts revealed that relative to placebo, thiopental significantly reduced [$F(1, 22) = 12.29$, $p < 0.01$, $\eta_p^2 = 0.36$], and ketamine tended to reduce ($p = 0.07$) N2. While the difference between pre- and post-infusion N2 amplitude was significant for the thiopental

session ($p = 0.05$, $\eta_p^2 = 0.17$), no significant differences were found between the effects of thiopental and ketamine on N2.

ERPs to novel stimuli

P3a amplitude

The primary finding was a significant drug type \times electrode \times time interaction [$F(4, 88) = 6.21$, $p = 0.001$,

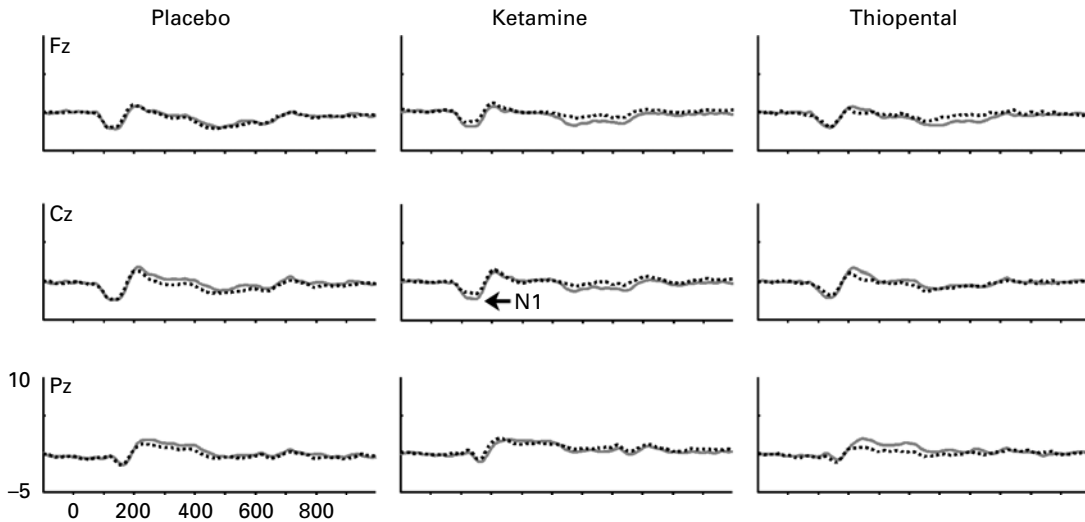


Figure 4. Pre-infusion (—) and post-infusion (·····) grand-average ERP waveforms elicited by standard stimuli at Fz, Cz, and Pz.

$\eta_p^2=0.22$). Pre-infusion P3a amplitude was significantly greater (at Fz and Cz) for the placebo session than for the two active drug sessions ($p < 0.05$ in both cases). Significant differences in pre- and post-infusion P3a amplitude were found at electrode Cz for all three conditions ($p \leq 0.05$ in each case) and at electrode Pz for the two active drugs ($p \leq 0.001$ in each case). However, significant differences in the magnitude of these P3a changes were found between placebo and the active drugs. The results of pairwise interaction contrasts are as follows.

Ketamine vs. placebo. There was a significant drug type \times electrode \times time interaction [$F(2, 44) = 11.10, p = 0.001, \eta_p^2 = 0.34$]. Relative to placebo, ketamine significantly reduced P3a amplitude at Pz [$F(1, 22) = 7.39, p = 0.01, \eta_p^2 = 0.25$] but significantly increased its amplitude at Fz [$F(1, 22) = 4.78, p = 0.04, \eta_p^2 = 0.18$]. However, this frontal increase was only significant when comparing the magnitude of effects for placebo and ketamine. The increase in frontal P3a amplitude within the ketamine session itself failed to reach significance.

Thiopental vs. placebo. There was a significant drug type \times electrode \times time interaction [$F(2, 44) = 7.51, p < 0.01, \eta_p^2 = 0.26$]. Relative to placebo, thiopental significantly reduced P3a amplitude at Pz [$F(1, 22) = 13.65, p = 0.001, \eta_p^2 = 0.38$].

Ketamine vs. thiopental. There was a significant drug type \times time interaction [$F(1, 22) = 4.16, p = 0.05, \eta_p^2 =$

0.16]. Averaged across electrodes, thiopental reduced P3a amplitude significantly more than ketamine.

P3a latency

There was a significant drug type \times time interaction [$F(2, 44) = 3.71, p = 0.04, \eta_p^2 = 0.14$]. Ketamine (but not thiopental or placebo) significantly reduced P3a latency from pre- to post-infusion ($p < 0.01, \eta_p^2 = 0.37$). Interaction contrasts also revealed that the magnitude of ketamine's effect on P3a latency was significantly greater than thiopental's [$F(1, 22) = 8.48, p < 0.01, \eta_p^2 = 0.28$] and trended to be larger than placebo's ($p = 0.06$). No significant differences were found between the effects of thiopental and placebo on P3a latency.

N2 amplitude

There were significant drug type \times time [$F(2, 44) = 7.69, p < 0.01, \eta_p^2 = 0.26$], and drug type \times electrode \times time [$F(4, 88) = 4.91, p < 0.01, \eta_p^2 = 0.18$] interactions. Both active drugs led to significant pre- to post-infusion changes in N2 amplitude ($p \leq 0.001$ in both cases). Interaction contrasts revealed that the magnitude of N2 attenuation was greater for both active drugs than for placebo ($p < 0.05$ in both cases). However, ketamine produced a significantly greater level of attenuation of N2 amplitude than thiopental [$F(1, 22) = 4.72, p = 0.04, \eta_p^2 = 0.18$]. Analysis of the three-way interaction revealed that relative to placebo, ketamine significantly reduced N2 amplitude at all three electrodes,

Table 2. Drug effects on ERPs to target, novel, and standard stimuli

Stimulus	Component	Drug type	Electrode	Mean amplitude (s.e.) in μV			Peak latency (s.e.) in ms		Primary latency effects	
				Pre-infusion	Post-infusion	Primary amplitude effects	Pre-infusion	Post-infusion		
Target	P3b	Placebo	Fz	6.3 (1.1)	6.8 (1.2)	Drug \times time; \times electrode interaction ($p=0.05$): Relative to placebo, both ketamine ($p=0.02$) and thiopental ($p=0.001$) attenuate P3b amplitude at Pz	395.9 (9.6)	410.7 (14.1)	n.s.	
			Cz	12.0 (1.5)	10.1 (1.4)		382.2 (8.7)	404.2 (11.8)		
			Pz	17.7 (1.5)	16.1 (1.5)		394.7 (8.5)	413.8 (10.9)		
		Ketamine	Fz	4.9 (1.0)	5.4 (1.0)		382.6 (10.4)	379.0 (9.3)		
			Cz	11.0 (1.5)	7.6 (1.3)		394.8 (11.8)	399.0 (12.5)		
			Pz	16.7 (1.5)	12.5 (1.4)		401.0 (11.1)	417.2 (13.9)		
		Thiopental	Fz	4.7 (1.1)	4.1 (0.9)		386.6 (8.8)	362.0 (10.1)		
			Cz	10.4 (1.5)	6.6 (1.5)		394.5 (8.4)	393.0 (11.4)		
			Pz	16.2 (1.5)	10.8 (1.4)		394.2 (5.9)	430.0 (10.4)		
	N2	Placebo	Fz	-3.7 (.9)	3.9 (0.8)	Drug \times time interaction ($p=0.02$): Relative to placebo, both thiopental ($p<0.01$) and ketamine ($p=0.07$) attenuate N2 amplitude	Not measured	Not measured		
			Cz	-5.2 (1.5)	-6.3 (1.2)					
			Pz	-0.9 (1.2)	-2.2 (1.1)					
		Ketamine	Fz	-4.8 (.9)	-2.8 (0.9)					
			Cz	-5.4 (1.4)	-4.3 (0.9)					
			Pz	-1.1 (1.3)	-1.0 (0.8)					
Thiopental		Fz	-5.0 (1.0)	-3.1 (1.1)						
		Cz	-6.2 (1.4)	-3.2 (1.0)						
		Pz	-2.3 (1.4)	-0.5 (0.8)						
Novel	P3a	Placebo	Fz	8.6 (1.3)	7.7 (1.0)	Drug \times time \times electrode interaction ($p=0.001$): Relative to placebo, both ketamine ($p=0.01$) and thiopental ($p=0.001$) attenuate P3a amplitude at Pz; and at Fz ketamine leads to a relative increase in P3a amplitude	366.1 (7.8)	366.5 (10.0)	Drug \times time interaction ($p=0.04$): Ketamine attenuates P3a latency relative to thiopental ($p=0.01$) and placebo ($p=0.06$).	
			Cz	14.6 (1.6)	12.2 (1.5)		348.4 (5.8)	342.2 (8.9)		
			Pz	14.9 (1.4)	13.6 (1.3)		359.4 (6.2)	352.0 (9.5)		
			Ketamine	Fz	6.5 (1.3)		7.3 (1.1)	373.1 (9.0)		345.2 (9.0)
				Cz	12.3 (1.7)		10.0 (1.5)	352.6 (6.4)		330.9 (7.3)
				Pz	13.0 (1.4)		9.2 (1.3)	356.4 (7.4)		321.2 (9.3)
		Thiopental	Fz	6.9 (1.3)	5.4 (1.0)		Drug \times time interaction ($p=0.05$): Thiopental attenuates P3a amplitude relative to ketamine ($p=0.05$) and placebo ($p=0.055$).	373.1 (8.0)		366.9 (13.2)
			Cz	12.2 (1.4)	8.2 (0.8)			352.6 (7.2)		344.0 (10.1)
			Pz	13.6 (1.3)	8.1 (0.9)			349.1 (8.3)		347.5 (8.9)

N2	Placebo	Fz	-5.9 (1.1)	-5.9 (1.0)	-5.9 (1.1)	Drug × time interaction ($p < 0.01$): Thiopental attenuates N2 amplitude relative to placebo ($p = 0.03$); ketamine attenuates N2 amplitude relative to both placebo ($p < 0.01$) and thiopental ($p = 0.04$).	Not measured	Not measured	Not measured
		Cz	-4.7 (1.1)	-4.9 (1.0)	-4.7 (1.1)				
		Pz	0.01 (0.9)	-0.7 (1.0)	0.01 (0.9)				
		Fz	-1.9 (0.9)	-7.4 (0.9)	-1.9 (0.9)				
		Cz	-0.6 (0.8)	-5.6 (0.9)	-0.6 (0.8)				
		Pz	1.3 (0.7)	-1.4 (1.1)	1.3 (0.7)				
	Thiopental	Fz	-3.3 (0.8)	7.5 (1.1)	-3.3 (0.8)				
		Cz	-2.5 (0.6)	-6.0 (0.8)	-2.5 (0.6)				
		Pz	-0.58 (0.6)	-1.1 (0.9)	-0.58 (0.6)				
		Fz	-2.4 (0.3)	-2.7 (0.3)	-2.4 (0.3)				
		Cz	2.7 (0.5)	-2.8 (0.4)	2.7 (0.5)				
		Pz	-1.8 (0.4)	-1.7 (0.4)	-1.8 (0.4)				
Standard N1	Placebo	Fz	-1.9 (0.3)	-2.6 (0.3)	-1.9 (0.3)	Drug × time interaction ($p = 0.03$): Ketamine attenuates N1 amplitude relative to placebo ($p = 0.03$) and thiopental ($p = 0.03$).	Not measured	Not measured	Not measured
		Cz	-2.2 (0.4)	-3.0 (0.4)	-2.2 (0.4)				
		Pz	-1.2 (0.3)	-2.0 (0.4)	-1.2 (0.3)				
		Fz	-2.3 (0.4)	-2.4 (0.3)	-2.3 (0.4)				
		Cz	-2.4 (0.4)	-2.5 (0.4)	-2.4 (0.4)				
		Pz	-1.7 (0.4)	-1.5 (0.4)	-1.7 (0.4)				
	Ketamine	Fz	-2.4 (0.3)	-2.6 (0.3)	-2.4 (0.3)				
		Cz	-2.2 (0.4)	-3.0 (0.4)	-2.2 (0.4)				
		Pz	-1.2 (0.3)	-2.0 (0.4)	-1.2 (0.3)				
		Fz	-2.3 (0.4)	-2.4 (0.3)	-2.3 (0.4)				
		Cz	-2.4 (0.4)	-2.5 (0.4)	-2.4 (0.4)				
		Pz	-1.7 (0.4)	-1.5 (0.4)	-1.7 (0.4)				

Table 3. Other significant effects from overall ANOVAS

Stimulus	Component	Effect	Effect size
Standard	N1 amplitude	Electrode**	0.28
		Time*	0.20
Target	P3b amplitude	Electrode***	0.70
		Drug***	0.28
		Time***	0.49
		Electrode × time***	0.56
		Electrode**	0.28
		Time**	0.35
	P3b latency	Electrode × drug*	0.14
		Electrode × time**	0.24
		Electrode***	0.32
Novel	P3a amplitude	Electrode***	0.61
		Drug**	0.25
		Time**	0.33
		Electrode × drug*	0.11
		Electrode × time***	0.43
		Electrode**	0.28
	P3a latency	Time**	0.35
	N2 amplitude	Electrode*	0.18
		Time***	0.57
		Electrode × time**	0.24

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

whereas thiopental significantly reduced N2 at only Fz and Cz.

N1 to standard stimuli

The primary finding was a significant drug type × time interaction on N1 amplitude to standard stimuli [$F(2, 44) = 3.71$, $p = 0.03$, $\eta_p^2 = 0.14$]. Ketamine (but not thiopental or placebo) significantly attenuated N1 amplitude from pre- to post-infusion ($p < 0.01$, $\eta_p^2 = 0.37$). Interaction contrasts also revealed that the magnitude of this effect was greater for ketamine than placebo [$F(1, 22) = 5.23$, $p = 0.03$, $\eta_p^2 = 0.19$] and thiopental [$F(1, 22) = 5.65$, $p = 0.03$, $\eta_p^2 = 0.20$]. The effects of thiopental and placebo did not significantly differ.

Relationship between changes in P3a/b amplitude and target RT

There were significant correlations between changes in both P3a and P3b amplitudes and changes in target RTs following the infusion of thiopental, but not ketamine. Specifically, delays in target RT following thiopental (but not ketamine), were significantly correlated with attenuations of target P3b ($r = -0.60$,

Table 4. Summary of the post-infusion effects of ketamine and thiopental

Stimulus	Component	Drug type	Effect
Target	P3b	Ketamine	Slows target response time (RT) relative to placebo Attenuates P3b amplitude at Pz relative to placebo Changes in target RT not significantly correlated with changes in P3b amplitude
		Thiopental	Slows target RT relative to both placebo and ketamine (trend) Attenuates P3b amplitude at Pz relative to placebo Changes in target RT correlated with changes in P3b amplitude
	N2	Ketamine	Trend to attenuate N2 amplitude relative to placebo
		Thiopental	Attenuates N2 amplitude relative to placebo
Novel	P3a	Ketamine	Attenuates P3a amplitude at Pz relative to placebo Increases P3a amplitude at Fz relative to placebo Decreases P3a latency relative to thiopental and placebo (trend) Changes in target RT not significantly correlated with changes in P3a amplitude
		Thiopental	Attenuates P3a amplitude at Pz relative to placebo Overall P3a attenuation greater than for ketamine Does not significantly alter P3a latency Changes in target RT correlated with changes in P3a amplitude
	N2	Ketamine	Attenuates N2 amplitude relative to both placebo and thiopental
		Thiopental	Attenuates N2 amplitude relative to placebo
	Standard	N1	Ketamine
Thiopental			n.s.

$p < 0.001$) and novelty P3a ($r = -0.50$, $p < 0.001$) amplitudes at electrode Pz.

Relationships between changes in ERP component amplitude

There were no significant correlations between changes in N1 amplitude to standard stimuli following either ketamine or thiopental and changes in either P3a or P3b amplitudes. Changes in N1 amplitude were also not significantly correlated to changes in the N2 amplitude to target or novel stimuli (although the relationship between N1 change and Novelty N2 change following thiopental reached the trend level, $r = 0.38$, $p = 0.08$). Similarly, changes in N2 amplitude to target and novel stimuli were not significantly correlated with changes in P3a or P3b amplitudes following either drug. However, the amount of attenuation in Target and Novelty N2 amplitude was correlated for both ketamine ($r = 0.5$, $p < 0.05$) and thiopental ($r = 0.48$, $p < 0.05$). Similarly, there were significant correlations in P3a and P3b attenuations following both ketamine ($r = 0.43$, $p < 0.05$) and thiopental ($r = 0.47$, $p < 0.05$).

Discussion

Table 4 presents a summary of the primary ERP and behavioural effects.

Target processing effects

Consistent with previous studies of ketamine and GABA agonists (Ahn et al., 2003; Hayakawa et al., 1999; Oranje et al., 2000; Reinsel et al., 1991; Rockstroh et al., 1991), we found that both ketamine and thiopental attenuated parietal P3b amplitude. Overall, the data suggest a role of both the NMDA and GABA-A receptor systems in the modulation of Target P3b. Interestingly, whereas we found that thiopental affected P3b amplitude but not its latency, a previous report found a different barbiturate affected P3b latency but not its amplitude (Fowler and Mitchell, 1997). However, a combination of drug, dose, and task differences between the two reports may have contributed to the conflicting results.

Both drugs also tended to attenuate Target N2, although this effect only reached significance for thiopental. N2 is frequently interpreted as an index of response inhibition (Falkenstein, 2006; Falkenstein et al., 1999) and/or conflict monitoring (Donkers and van Boxtel, 2004; Nieuwenhuis et al., 2003; Van Veen and Carter, 2002a,b) mediated by the anterior cingulate cortex (ACC) and other prefrontal regions (Bekker et al., 2005; Jonkman et al., 2007; Mathalon et al., 2003; Van Veen and Carter, 2002a,b). Accordingly, the effects of ketamine and thiopental on N2 amplitude might result from the disruption of ACC activity

required for the detection and processing of infrequent target stimuli.

Overall, the data indicate that ketamine and thiopental had similar effects on ERP correlates of target processing. Additionally, both drugs led to significant delays in RT to target stimuli, suggesting that their basic behavioural consequences were also similar. However, thiopental exhibited a trend to slow target RT more than ketamine. In addition, P3b amplitude attenuations following thiopental, but not ketamine, were significantly correlated with a slowing of RT to target stimuli. Thus, the active drugs were dissociable in terms of the coupling of the P3b changes with behavioural slowing.

Novelty processing effects

The data also suggest a role of both the NMDA and GABA-A receptor systems in the modulation of Novelty P3a. This is one of the first reports to demonstrate that these drugs attenuate parietal P3a amplitude. However, although their effects overlapped, ketamine and thiopental appeared to produce at least partially dissociable effects on the neural correlates of novelty processing. While thiopental led to attenuation of parietal P3a compared to placebo, it also led to a greater overall reduction in P3a than ketamine. Moreover, P3a amplitude attenuations following thiopental, but not ketamine, were significantly correlated with a slowing of RT to target stimuli.

In addition to attenuating parietal P3a, ketamine led to other alterations in P3a topography and latency. First, ketamine led to a significant reduction in overall P3a latency relative to thiopental and a trend level reduction relative to placebo. Reduced P3 latencies are often interpreted as an index of enhanced processing speed or stimulus classification speed in healthy adults (see Picton, 1992). Thus, although speculative, one possible explanation of P3a latency reductions following ketamine is that NMDA antagonism alters the speed with which novel stimuli are processed. In addition, ketamine attenuated Novelty N2 amplitude to a greater extent than both thiopental and placebo. Finally, it produced a small but significant increase in frontal P3a amplitude relative to placebo, although it is important to note that the simple contrast comparing Fz amplitude from pre- to post-infusion in the ketamine sessions failed to reach significance. In all, the effects of NMDA antagonism on the early (indexed by N2) and later (indexed by changes in P3a amplitude, topography, and latency) correlates of novelty processing appeared to be more varied than the effects of GABA-A agonism.

Standard stimulus processing effects

We found that ketamine attenuated N1 amplitude to standard stimuli significantly more than both thiopental and placebo. A number of previous ERP studies have suggested that the N1 component reflects pre-attentive sensory processing or early selective attentional processing (Coull, 1998; Hillyard et al., 1973; Muller-Gass and Campbell, 2002). Thus, in addition to its effects on target and novelty processing, ketamine (but not thiopental) affected early sensory processing of frequent visual stimuli. However, the degree of N1 attenuation following ketamine was *not* significantly correlated with the degree of attenuation of either Target/Novelty N2 amplitude or P3a/b amplitude. Thus, the basic sensory processing effects of ketamine appear to be dissociable from the effects of the drug on later, cognitive processing of target and novel stimuli.

Summary

Thiopental attenuated Target and Novelty N2 amplitude, attenuated parietal P3a and P3b amplitudes, but had no other significant effects on P3a/b topography or latency. Thiopental also tended to slow RTs more than ketamine. Finally, the degree of both P3a and P3b attenuations following thiopental (but not ketamine) were strongly correlated with delays in RTs to target stimuli. Taken together, these data suggest stimulating GABA-A receptors produces a general dampening of cortical information processing that is reflected in attenuations in the Target and Novelty N2, and in P3a/b attenuations that are associated with slower responses. As GABA is the primary inhibitory neurotransmitter in the human cortex, thiopental's effects may simply represent a generalized increase in inhibition of neural activity across the cortical generators responsible for the P3 complex. This broad inhibition could have led to the rather uniform decreases in the 'signal' of the ERP correlates of target and novelty processing that we found here, which were in turn coupled with slowed behavioural responses.

Ketamine also affected target processing, but appeared to have more varied effects on the neural correlates of novelty processing. Ketamine attenuated the parietal P3b elicited by target stimuli, but had no significant effects on P3b latency. In contrast, ketamine attenuated parietal P3a amplitude, reduced P3a latency, and relative to changes in the placebo condition, increased frontal P3a amplitude. In addition, ketamine attenuated Novelty N2 (but not Target N2) amplitude significantly more than thiopental or placebo. Overall, while the data support previous findings that

ketamine affects the neural correlates of target processing (Ahn et al., 2003; Oranje et al., 2000), they are also consistent with previous reports in both the human and animal literatures describing the importance of the NMDA system in novelty processing (Gironi Carnevale et al., 1990; Grunwald and Kurthen, 2006; Harich et al., 2007).

One possible way that ketamine affects novelty processing is by altering the perceptual relationships of the different categories of stimuli in the oddball task. For example, it has been demonstrated that the relationship between target and non-target (standard) stimuli strongly influences the P3a component (see Polich, 2007). Specifically, when it is difficult to discriminate between target and non-target stimuli, P3a amplitude increases and latency decreases (Polich and Comerchero, 2003). If ketamine alters the perceived relationship between the target (large blue circle) and standard stimuli (small blue circle) in the oddball task, it could potentially account for the P3a latency reductions found here. However, this interpretation should be regarded as speculative, as attenuations in N2 and P3a amplitude following ketamine suggest that NMDA antagonism affected multiple cognitive operations related to novelty processing.

Although speculative, ketamine could affect processing in the oddball task by altering components of not only glutamate but also GABA neurotransmission (Krystal et al., 2003a). This could have resulted in alterations of the 'tone' of synchronous activity in the prefrontal cortex (Rao et al., 1999, 2000), a region which is important for both P3a and P3b (Knight, 1984, 1996; Soltani and Knight, 2000) and is known to be affected by ketamine (Honey et al., 2004, 2005). As opposed to the generalized inhibition caused by thio-pental, these disruptions in the prefrontal cortex and other regions could result in more varied changes in the efficiency with which the cortex processes rare, engaging cognitive stimuli.

Limitations

It should be noted that this study was intended to be primarily exploratory, and has several limitations. First, we only studied the effects of a single dose of ketamine and thio-pental. Accordingly, it is not possible to determine from the current data if the GABA-A and NMDA receptor effects on the P3 complex vary in a dose-dependent manner. Second, the oddball task used in this report is limited in terms of the behavioural dependent variables it generates. For example, participants did not respond to novel stimuli in any way and it was therefore impossible to directly

determine if novelty processing speed was affected by ketamine. In the future, the effects of these drugs on the ERP correlates of cognitive processing should be studied with more complex and behaviourally rich paradigms.

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Statement of Interest

Dr Krystal has served as a paid scientific consultant for years 2005, 2006, 2007 and 2008 to: Astra Zeneca, Bristol-Myers Squibb, Cypress Bioscience Inc., Eli Lilly and Co., Forest Laboratories Inc., GlaxoSmith-Kline, Houston Pharma, Janssen Research Foundation, Lohocla Research Co., Merz Pharmaceuticals, Organon Pharmaceuticals Inc., Pfizer Pharmaceuticals, Sumitomo Pharmaceuticals America Ltd, Takeda Industries, Tetrigenex Pharmaceuticals, and Transcept Pharmaceuticals. He is also co-sponsor of three pending patents related to the use of glutamatergic agents to treat psychiatric disorders and antidepressant effects of oral ketamine. Dr Petrakis holds a grant funded through Forest Laboratories Inc. Dr Mathalon holds a grant funded through Astra Zeneca.

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