Overnight transdermal scopolamine patch administration has no clear effect on cognition and emotional processing in healthy volunteers

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Abstract

There has been increasing interest in the antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine. Here we assess, for the first time, whether a transdermal scopolamine patch is sufficient to induce changes in cognition that are consistent with the reported cognitive and antidepressant effects of scopolamine. A scopolamine or placebo patch was administered to healthy volunteers [n=33] for 17h in a double-blind, between-subject procedure. There was no clear effect of scopolamine patch on emotional cognition, verbal or working memory, suggesting that the effective dose of scopolamine available through the patch is too low to represent a viable antidepressant mechanism.

Introduction

Hyperactivity in the muscarinic cholinergic receptor system has been implicated in the pathophysiology of depression and there is growing interest in whether the nonspecific antagonist scopolamine has potential as an antidepressant treatment (Drevets et al., 2013). Scopolamine induces reproducible, transient deficits across multiple cognitive domains in animals and humans (Ghoneim and Mewaldt, 1975) and produces a rapid antidepressant effect in depressed patients when administered intravenously (Furey and Drevets, 2006, but see Park et al., 2018). Biases in the processing of emotional information, in particular increased processing of negative stimuli, are core cognitive markers of depression. Acute antidepressant administration modulates these biases in patients and healthy volunteers, and these early effects are predictive of treatment response (Harmer et al., 2017). Here, we assess the effect of a transdermal scopolamine patch (licensed for travel sickness) on emotional processing. It was predicted that the patch would induce a positive emotional cognitive bias, consistent with scopolamine's antidepressant effects. Measures of non-emotional cognition were included as a positive control, and it was predicted that scopolamine would have a generalised detrimental effect on verbal and working memory.

Methods

Thirty-three healthy participants were administered either a Scopoderm TTS (scopolamine 1.5mg) or placebo patch, which was applied to the upper arm for 17 hours in a double-blind, randomised procedure. Exclusion criteria included: past/current Axis 1 DSM-V psychiatric disorder, BMI<19/>30, >5 cigarettes/day, medical contraindication to scopolamine, family history of bipolar disorder. Following overnight patch administration, emotional cognition was measured using the P1vital® Oxford Emotional Test Battery (ETB) - a set of five tasks that have been well validated in healthy volunteers and depressed patients to detect early effects of

antidepressant drugs on emotional processing (Harmer et al., 2017). Verbal and working memory was measured using the Auditory Verbal Learning Test (AVLT) and N-Back task. Side effects and subjective mood (Spielberger State Anxiety Inventory (STAI-S), Positive and Negative Affect Scale (PANAS), Befindlichkeit Scale (BFS)) were measured at three points (baseline, pre- and post-testing). At the end of cognitive testing, participants provided a randomisation guess and the patch was removed.

Demographic and baseline characteristics were analysed with independent samples t-tests. Questionnaire, ETB, AVLT, and N-Back data were analysed using repeated measures ANOVA. Facial Expression Recognition Task data was missing from one participant (scopolamine).

Results

There were no significant differences between groups in age, gender, verbal IQ, and baseline neuroticism, depression and trait anxiety (all p's>0.1). There was no significant effect of group on state measures of anxiety, affect, mood and energy (all p's>0.1). Dry mouth was reported significantly more in the scopolamine group (62.5% vs. 23.5%, $\chi(1) = 5.125, p=0.037$), but there were no other significant group differences in side effects. Randomisation guesses suggested that participants were significantly better than chance at guessing group allocation (correct guess: 62.5% scopolamine group, 76.5% placebo group, $\chi(1) = 5.125, p=0.037$). There were no significant group effects on facial expression recognition, emotional word categorization/recognition or attentional vigilance to emotional faces (Table 1). There was a significant group x word valence interaction on the emotional recall task [$F(1,31)=5.652, p=0.024$], which reflected relatively reduced recall of positive words and increased recall of negative words in the scopolamine group (Fig.1). However post-hoc tests demonstrated no significant group differences for positive [$t(31)=-0.681$, $p=0.501$] or negative [$t(31)=1.632, p=0.113$] words. There was no significant group effect on the AVLT (number of words recalled blocks 1-5, group x block

interaction F(4,124)=1.35,p=0.37) or N-back task (Accuracy: F(1.28)=0.840,p=0.37; Reaction time: F(1,28)=0.380,p=0.54).

Conclusions

This study evaluated the effect of the scopolamine patch in healthy participants on a battery of measures that have previously been shown to be sensitive to the effects of acute antidepressant administration in healthy volunteers (Harmer et al., 2017). Contrary to the study predictions, we found no clear effect of the scopolamine patch on emotional processing. There was a weak effect of scopolamine on emotional memory, but in the opposite direction to that seen with classic antidepressants, which typically act to increase positive memories. Further, scopolamine did not impair cognitive performance on tests of verbal and working memory, which is contrary to the well documented cognition-impairing effects of scopolamine in animal and human models, even using similar testing paradigms and transdermal application (Parrott, 1986). Whilst the lack of effects of the scopolamine patch on cognition will be of interest to users of the patch for travel sickness, these findings do suggest that the effective dose of scopolamine available through the patch is too low to represent a viable antidepressant mechanism. Although blood scopolamine levels were not measured in this study, previous studies suggest that the peak concentration of scopolamine achieved by the patch (~100 pg/ml plasma concentration reached after 8 hours) is much lower than that induced by the standard 4.0 µg/kg intravenous antidepressant dose (~18ng/ml serum concentration within minutes, dropping to ~2ng/ml after 1 hour) (Renner et al. 2006, Pihlajamaki et al. 1986). These findings should be interpreted in the context of the modest sample size and with the caveat that healthy volunteer models may be less sensitive than patient samples to detect the antidepressant effects of scopolamine.

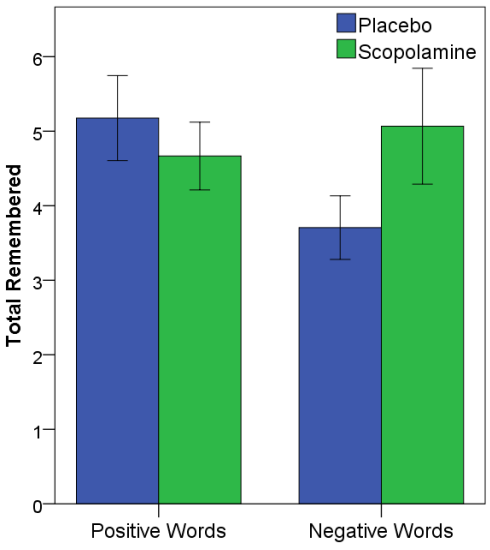
Table One: Mean scores on emotional tasks in scopolamine and placebo treated groups.

	Measure	Task Condition	Scopolamine (N=16)	Placebo (N=17)	Statistics (*p*)
Facial Emotion Recognition	Accuracy [total correct]	Neutral	7.19 (1.52)	7.41 (1.33)	0.66
		Anger	19.62 (2.39)	20.35 (4.27)	
		Disgust	19.75 (5.24)	21.88 (5.38)	
		Fear	21.06 (3.89)	18.76 (5.46)	
		Happiness	26.25 (4.37)	26.24 (2.95)	
		Sadness	21.25 (6.88)	20.18 (4.49)	
		Surprise	20.69 (6.60)	21.18 (4.39)	
	Reaction Time [msec]	Neutral	1606.93 (452.32)	1513.83 (300.13)	0.32
		Anger	1858.25 (336.72)	1671.86 (304.27)	
		Disgust	1778.61 (355.75)	1662.650 (499.00)	
		Fear	2023.21 (372.90)	1856.42 (257.43)	
		Happiness	1519.10 (203.93)	1479.67 (152.06)	
		Sadness	1827.33 (266.40)	1769.78 (402.58)	
		Surprise	1707.88 (255.26)	1724.05 (277.02)	
Emotional Categorisation	Accuracy [total correct]	Positive	29.31 (0.70)	29.06 (0.66)	0.98
		Negative	28.94 (1.12)	29.18 (0.88)	
	Reaction Time [msec]	Positive	923.60 (168.15)	899.39 (141.61)	0.66
		Negative	965.98 (165.92)	943.17 (145.32)	
Emotional Recall	Total Items Recalled	Positive	4.69 (1.70)	5.18 (2.35)	0.02[a]
		Negative	5.06 (2.91)	3.71 (1.76)	
Emotional Recognition	Accuracy [total correct]	Positive	23.75 (3.30)	25.12 (2.93)	0.1
		Negative	21.06 (4.70)	23.29 (2.73)	
	Reaction Time [msec]	Positive	1478.03 (436.73)	1295.56 (256.77)	0.22
		Negative	1468.53 (358.95)	1365.37 (253.79)	

Attentional Vigilance (msec)	Masked	Positive	-14.04 (46.99)	-6.25 (48.75)	0.94
		Negative	-0.55 (34.17)	5.63 (20.45)	
	Unmasked	Positive	-0.93 (37.8)	-11.37 (72.65)	0.44
		Negative	13.5 (43.77)	-13.41 (25.88)	

Values represent the mean with standard deviation in parentheses. Task data were analysed using repeated measures analysis of variance (ANOVA) with group as a between-subjects factor (placebo, scopolamine) and task condition as a within-groups factor. The *p* values displayed are for the group x condition interaction. ($^{a}p<0.05$).

Figure One: Emotional Memory Task: Mean number of correctly remembered positive and negative words as compared between the drug and placebo groups. [Error bars: +/- 1SE]



Declaration of conflicting interests

MB is employed on a part time basis by P1vital Ltd. He has received travel expenses from Lundbeck and acted as a consultant for J&J. CJH has received consultancy fees from P1vital, Lundbeck, Servier and J&J and holds grant income from UCB. SEM has received consultancy fees from P1Vital and J&J and holds grant income from UCB and J&J. PJC and BB report no conflicts of interest.

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