

The effect of transdermal nicotine patches on sleep and dreams

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Received 7 February 2005; received in revised form 13 February 2006; accepted 18 April 2006

Abstract

This study was undertaken to determine the effect of 24-h transdermal nicotine patches on sleep and dream mentation in 15 smokers aged 20 to 33. Utilising a repeated measures design, it was found that more time awake and more ASDA micro-arousals occurred while wearing the nicotine patch compared to placebo. Also, the percentage of REM sleep decreased, but REM latency and the proportion of time spent in NREM sleep stages did not change significantly. Dream reports containing visual imagery, visual imagery ratings and the number of visualizable nouns were significantly greater from REM compared to Stage 2 awakenings, regardless of patch condition. However, a general interaction effect was observed. Stage 2 dream variables remained equivalent across nicotine and placebo conditions. Within REM sleep, more dream reports containing visual imagery occurred while wearing the nicotine patch, and these were rated as more vivid. The greater frequency of visual imagery reports and higher imagery ratings specifically from REM sleep suggests that previously reported dreaming side effects from 24-h nicotine patches may be specific to REM sleep. Combined with previous animal studies showing that transdermally delivered nicotine blocks PGO activity in REM sleep, the current results do not appear consistent with PGO-based hypotheses of dreaming, such as the Activation-Synthesis (AS) or Activation, Input and Modulation (AIM) models.

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Keywords: Sleep; Dreams; Transdermal nicotine patches; Ponto-geniculo-occipital (PGO) waves; Arousal

1. Introduction

The concept of mind–body isomorphism, denoting similarity of form between psychological and physiological events, has been explicit in dream formation hypotheses since psychoanalytic dream theory and is fundamental to modern theories of dreaming [1]. The activation synthesis (AS) model of dreaming developed by Hobson and McCarley [2] and since revised into the Activation, Input and Modulation (AIM) model [3] is perhaps the most comprehensive attempt to draw together the physiological and psychological aspects of sleep and dreaming. The AIM model emphasises a shift from aminergic modulation in waking to the dominance of cholinergic neuromodulation during REM, and the presence of ponto-geniculo-occipital (PGO) waves, which is argued to be a key characteristic of

dreaming. However, the relationship of PGO waves to dreaming remains controversial [4]. In animal models, PGO waves have been shown to primarily exist during REM sleep [3]; however, PGO waves cannot yet be directly measured in humans, and therefore cannot be directly studied in relation to dream activity [4].

There is strong evidence which suggests that the trigger for the whole dream formation system, including the eye movement generator may be cholinceptive [3]. Injection of the cholinergic agent carbachol into the pontine reticular formation (PRF) in cats produced prolonged enhancement of REM sleep [1] and in humans the parenteral injection of the anticholinesterase agent physostigmine potentiated REM and these episodes were associated with hallucinoid dreaming [5]. McCarley [6] reported that the local injection of a cholinergic agonist to the PRF reliably induced a phenomenologically complete REM sleep-like state including muscle atonia, EEG desynchronisation, PGO waves, and rapid eye movements. Although such findings do not provide complete evidence that the PRF is the normal trigger zone and ACh is the normal neurotransmitter in

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the production of REM; the presence of ACh in the cortex [6] and the brainstem [7] during REM does suggest that natural REM does have a cholinergic component.

Due to this link between the cholinergic mechanisms and REM, a few studies have been conducted into the influence of the cholinergic agonist nicotine on sleep. However, these have produced varied results. An early study reported that pontine microinjections of nicotine had no effect on REM in cats [8], while another study, also on cats had demonstrated that nicotine, received subcutaneously, did induce REM sleep [9]. More recently, nicotine has been implicated in the regulation of PGO spikes with Vazquez et al. [10] finding that PGO spike activity was abolished in cats by the application of transdermal nicotine patches. Further research in rats found that subcutaneously delivered nicotine stimulated serotonergic neurons of the dorsal raphe nucleus (DRN) specifically during REM sleep, without any significant change during waking or NREM sleep [11]. 5HT DRN cells subsequently inhibit pedunculopontine (PPT) and laterodorsal tegmental (LDT) neurons which generate PGO waves. This action was confirmed in a study injecting nicotine into the DRN of rat midbrain slices and recording the firing rates of the DRN, LDT and PPT [12]. In summary, it seems that although the REM-sleep generator system at the PRF is activated cholinergically, subcutaneous nicotine inevitably acts at the DRN, which results in a serotonergic suppression of REM processes such as PGO waves.

The development of 24-h transdermal nicotine patches as an aid to smoking cessation presents an opportunity to study the impact of receiving nicotine throughout the night in humans. An interesting outcome from the use of such patches has been anecdotal reports of disrupted sleep and unusual or vivid dreaming [13], which have even been acknowledged as possible side-effects by manufacturers [14]. Interestingly, such anecdotal reports of vivid dreaming could be considered at odds with the animal research to date, as one would expect *less* vivid dreaming associated with patches proposed to *inhibit* PGO activity in cats and rats. Surprisingly, there has been relatively little research systematically investigating the effect of nicotine patches on dreams and sleep quality in humans.

Wetter et al. [15] found that wearing nicotine patches resulted in improvements in important polysomnographic measures of sleep quality, including a reduction in fragmentation and increased levels of slow wave sleep, compared to unmedicated quitting and pre-cessation measures, although they found no significant effect on REM sleep. Salin-Pascual and Drucker-Colin [16] found that transdermal application of nicotine increased REM time in both smokers and non-smokers. In other questionnaire-based investigations, the transdermal nicotine patch has been implicated in a dose-related increase in patient reports of mild to moderate sleep disturbance, insomnia and abnormal dreams [17]. Gillin et al. [18] found that transdermal nicotine applied to non-smoking volunteers was associated with early morning awakening and reduced REM sleep time in a dose-dependent fashion (across placebo, 7 mg and 14 mg patches). Although no significant effect on dreams was reported, this was merely observed from questionnaires

given the following morning. It is now well accepted that scientific investigation of dream mentation requires systematic awakenings from specific sleep stages throughout the night [19]. Furthermore, as acknowledged by Gillin et al. [18], the effects of nicotine patches on non-smokers may be problematic to extrapolate to smokers, as the pharmacokinetic and pharmacodynamic effects of transdermal nicotine differ between smokers and non-smokers [20,21].

As in waking, generalised cortical arousal in sleep occurs though the ascending reticular activating system (RAS) and Steriade [22,23] suggests that it is cholinergic RAS arousal that allows consciousness to exist in dreaming. Furthermore, there is substantial evidence to suggest that such cholinergic systems are the source of both waking and dream consciousness [24]. A finding that cholinergic agonist nicotine patches affect the quantity and quality of REM sleep mentation would suggest interaction with PGO waves and support the AIM model of dreaming. However, a change in mentation in both NREM and REM sleep while using the transdermal nicotine patches would more likely be due to stimulation of cholinergic RAS neurons involved in generalised cortical arousal.

The aim of this experiment was to investigate the effect of transdermal nicotine patches on sleep architecture and the subjective experience of dreaming in smokers. It was hypothesised that participants would experience more arousals and shorter sleep time while using the transdermal nicotine patch compared to the placebo patch condition. Based on anecdotal reports [13,17], it was expected that the mentation reports obtained from participants wearing the transdermal nicotine patch would include more visual imagery, be subjectively rated as more vivid, and contain more visualizable nouns than the mentation reports given under the placebo condition.

2. Methods

2.1. Participants

16 individuals volunteered to participate in this study, and were fully informed as to the nature and methods of the research. One participant withdrew before the completion of the data collection hence the sample size was reduced to nine males and six females between the ages of 20 and 33 ($M=25.82$, $S.D.=4.30$). Participants were all smokers who were otherwise of good health, with no known history of sleep disorders or skin or cardiovascular conditions that may have been complicated by the use of transdermal nicotine, and were not pregnant or breastfeeding. Participants were not paid for their involvement, but were allowed to keep the remaining six patches in their issued box of transdermal nicotine patches.

2.2. Materials

The polysomnography (PSG) recordings were collected using S-Series 16 channel Polygraph with W-Series Sleep/Replay display and analysis software (Compumedics Pty, Ltd.

Melbourne, Australia). Gold-plated electrodes (Model F-E5GH; Grass Instruments Co., CA), conductive electrode paste (Ten20, Grass Instruments Co.), surgical tape (Micropore, 3 M Pharmaceuticals) gauze swabs (7.5 × 7.5 cm, Smith and Nephew Pty Ltd) and skin cleansing alcohol swabs (Briemar Nominees Pty Ltd) were used for electrode preparation and placement.

Under both the experimental and control conditions participants wore a square of *Elastoplast*[®] adhesive dressing strip (Beiersdorf Australia, Ltd, NSW). On the experimental night a *Nicobate CQ*[®] 24-h transdermal nicotine patch (GlaxoSmithKline, 2001) of either 21 mg/24 h or 14 mg/24 h (if participant smoked less than 10 cigarettes/day on average) was placed under the dressing strip. Hence, participants wore dressing strip in both conditions and did not observe whether the nicotine patch was embedded on the strip beforehand. There was no way to see or feel the difference between the control and experimental strips. Participants' sleep was monitored in a sleep laboratory located at Monash University. The laboratory consists of two separate bedrooms each with private bathroom facilities, and a central control room from which the experimenter monitored the participants and communicated with each room through an intercom. All mentation reports were tape-recorded.

2.3. Design

A sample size of 15 participants, which is representative of sample sizes commonly used in experiments of this nature [19], was used in this study. The study utilised a repeated measures design, as the same subjects were exposed to both experimental patch and placebo control conditions, presented in a random order. This resulted in seven participants in the experimental patch condition first and eight placed in the placebo control condition first. Awakenings from REM and NREM Stage 2 were counterbalanced across subjects to control for time of the night effects.

2.4. Procedure

2.4.1. Recruiting and informing participants

Approval for this study was given by the Standing Committee on Ethics in Research Involving Humans at Monash University (Approval # 2002-182). Participants were recruited through campus posters and local advertisements. A number of exclusion criteria were required due to the use of nicotine, an addictive substance, in this study. People who were not permitted to participate included: (a) people with sleep disorders or those taking medication to induce or reduce sleepiness in any way, (b) people under 18, (c) those who could not give informed consent, (d) non-smokers, (e) those allergic to any component of the transdermal nicotine patch, or with a skin condition that the patch may have complicated, (f) pregnant or breastfeeding women, and (g) those who had suffered a recent stroke or heart attack.

After the procedure had been fully explained informed consent was obtained from each participant indicating their willingness to comply with the requirements of the study.

Participants were required to come into the university sleep laboratory for two sleep sessions, at least 1 week apart, 1 h before their usual bedtime to allow for electrode placement and experimental procedures, and ended the sleep period at their usual time of rising. Participants were asked to continue in their normal routine in the days leading up to each session, but were asked to cease smoking 2 h before coming in to the laboratory in order to ensure the level of nicotine in their blood was low. On arrival at the laboratory each participant had a square of dressing strip (either nicotine or placebo) applied to his or her skin by the experimenter, who was aware of the experimental conditions.

2.4.2. Placement of electrodes

A standard PSG recording montage was adopted [25]. EEG placements were to C3/A2 and C4/A1 locations according to the international ten–twenty system [26]. EOG placements were to the left and right outer canthi with each referenced to Fp [26]. EMG placements were at the left and right mentalis musculature. EEG traces were calibrated at 50 μV =1 cm with impedances below 5 M Ω .

2.4.3. Dream reports

Participants were woken no more than six times during the night, with half of these awakenings occurring in REM and half in Stage 2 sleep. These awakenings were counterbalanced with each participant randomly assigned to being awoken first in REM, then in Stage 2 or visa-versa. On the participant's second night this order was reversed.

To wake participants, the experimenter called their name through an intercom and asked if they were awake. Once the participant responded the experimenter asked: "Could you describe any thoughts or images that were going through your mind just before I called to you", then "Is there anything else you can remember?" If visual imagery was mentioned, the participants were then asked to rate the vividness of the imagery on a scale from 1 "least vivid—hardly memorable" to 10 "most vivid—like real". The question set was pre-recorded to eliminate any systematic bias that may have been produced unintentionally by the experimenter. The participants' responses were also recorded onto cassette tape. Participants were instructed to return to sleep immediately after questioning.

3. Results

Data for this study were collected in the form of polysomnography recordings of sleep for experimental and control nights for each participant and mentation reports from both REM and Stage 2 sleep under both conditions. The polysomnography records from the 15 participants were initially scored automatically using W-Series Sleep/Replay display and analysis software (Compumedics Pty, Ltd. Melbourne, Australia) in 30-s epochs using standard scoring criteria [25]. This data was then rescored visually by the experimenter and a sleep technologist with over 10 year's experience. Where discrepancies in scoring occurred, the sleep technologist's scoring was adopted. Repeated measures *t*-tests

were used to analyse differences between the experimental and control conditions in the percentage of time awake, in NREM sleep, REM sleep, arousals and REM latency. Repeated measures MANOVA and ANOVA were adopted in the statistical analysis dream report data.

3.1. Disruption of sleep

Under the experimental condition, many participants experienced a disrupted nights sleep with frequent arousals and periods of wakefulness. Frequent brief arousals have been found to increase daytime sleepiness without reducing total sleep time [27]. Therefore, the average number of micro-arousals as defined by the American Sleep Disorder Association [28] and the average time spent awake by each participant, as a percentage of the total time available for sleep (during “lights out”) under experimental and control conditions was calculated and is displayed in Table 1.

Wearing nicotine patches resulted in an increase in the average percentage of time available for sleep that participants spent awake ($M=14.82$, $S.D.=16.13$). This increase was significant, $t(14)=3.56$, $p<0.005$, two-tailed. Under the nicotine condition, participants experienced more micro-arousals per hour on average ($M=4.00$, $S.D.=5.62$), and this increase was also statistically significant, $t(14)=2.76$, $p<0.05$, two-tailed.

3.2. Sleep architecture

The amount of REM sleep experienced under control and experimental conditions, as a percentage of total sleep was calculated, along with the average percentage of total sleep time spent in NREM Stages 1 and 2 and slow wave sleep. These results are displayed in Fig. 1.

On the experimental night there was a decrease in the percentage of total sleep time spent in REM sleep ($M=6.68$, $S.D.=10.12$). This decrease was found to be significant, $t(14)=2.56$, $p<0.05$, two-tailed. No significant difference was found in the average amount of time spent in NREM Stages 1 and 2, $t(14)=0.11$, $p=0.92$, or SWS, $t(14)=1.75$, $p=0.10$, two-tailed.

The average REM latency from sleep onset for 14 participants on control ($M=94.82$, $S.D.=35.27$) and experimental nights ($M=110.82$, $S.D.=45.47$) was not significantly different, $t(13)=1.19$, $p=0.28$, two-tailed. One participant did not enter REM on the experimental night and therefore this case data was not included in the REM latency analysis.

Table 1

The average time spent awake as a percentage % of the total time available for sleep for participants on control and experimental nights

Condition	Average time awake (%)	Average micro-arousals/h	<i>n</i>
Control	16.79 (9.14)	15.44 (5.16)	15
Experimental	31.60 (19.42)	19.45 (7.47)	15

Also, the average number of micro-arousals per hour experienced by participants on control and experimental nights. Standard deviations for each mean are in brackets.

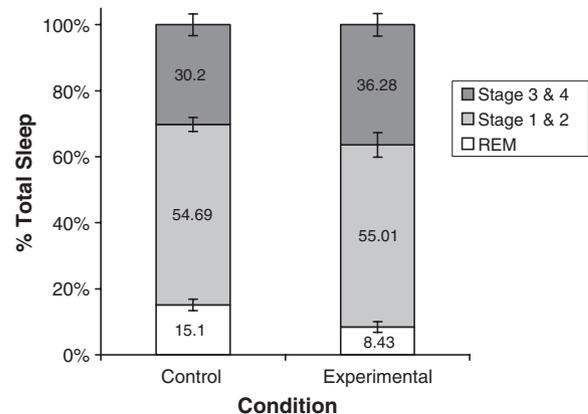


Fig. 1. The average percentage (%) of total sleep time spent in REM, NREM Stages 1 and 2 and Stages 3 and 4 (slow wave sleep; SWS) on control and experimental nights. Error bars represent standard error (S.E.) of the mean.

3.3. Dream report data

It was hypothesised that the mentation reports obtained from participants wearing the nicotine patch would include more visual imagery than the mentation reports given while not wearing the patch. This would be indicated by the presence of more mentation reports independently judged as containing imagery, more visualizable nouns, and higher in visual imagery self-rated by participants. The 120 scheduled awakenings across the 15 participants, was reduced to 109 reports from 14 participants. This was due to: (1) A participant falling asleep during questioning (2 reports), and (2) participants not reaching the desired sleep stages for conditions during the sleeping period (9 reports). This number of reports also includes reports removed due to matching. For example, if only the first REM report was achieved on the experimental night, only the first REM report from the placebo control night was used (and visa-versa).

The average time of waking for each experimental condition was as follows: Nicotine (REM: $M=3:57$ am, $S.D.=68.68$ min; Stage 2: $M=3:37$ am, $S.D.=127.40$ min), Placebo (REM: $M=4:34$ am, $S.D.=143.60$ min; Stage 2: $M=4:36$ am, $S.D.=153.99$ min). For average time of waking, a 2×2 repeated measures ANOVA showed no significant main effects for Condition (Nicotine vs. Placebo) $F(1,14)=1.67$, $p=0.217$, Sleep Stage (REM vs. Stage 2) $F(1,14)=0.27$, $p=0.217$; or Interaction (Condition \times Sleep Stage) $F(1,14)=0.34$, $p=0.57$.

Each report was rated as either (1) reporting a visual image, or (2) not reporting a visual image. Visual imagery was said to have been present if a visualizable noun was used in the mentation report. Visualizable nouns were defined as nouns of objects that could be seen as in waking life [19]. This scoring was then conducted by an independent judge, blind to conditions. The number of imagery reports divided by the number of awakenings for each subject in Stage 2 and REM sleep was calculated to determine the percentage of imagery reports per condition.

The dream report results are summarized in graphical form as the percentage of imagery reports per condition in Fig. 2, the average number of visualizable nouns per condition in Fig. 3,

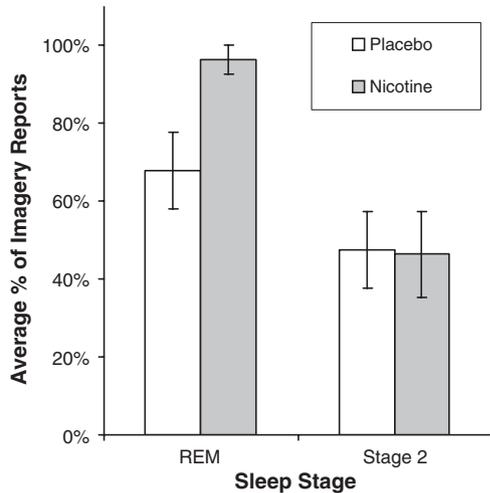


Fig. 2. The average percentage of mentation reports containing visual imagery, as judged by an independent rater (blind to conditions), from Stage 2 Nicotine, Stage 2 Placebo Control, REM Nicotine and REM Placebo Control conditions. Error bars represent standard error (S.E.) of the mean.

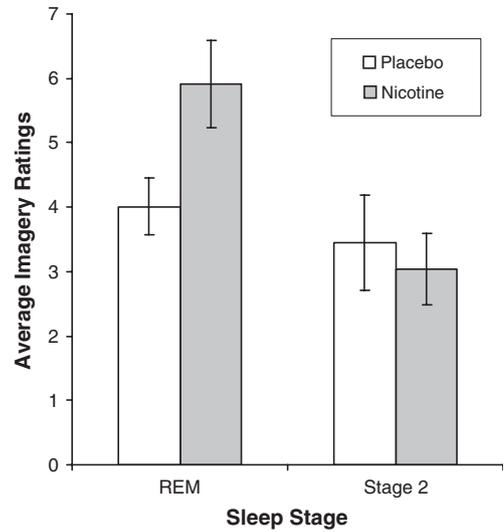


Fig. 4. The average imagery ratings of participants own mentation reports from Stage 2 Nicotine, Stage 2 Placebo Control, REM Nicotine and REM Placebo Control conditions. Ratings are scores out of 10. Error bars represent standard error (S.E.) of the mean.

and the average visual imagery ratings of subjects own reports per condition in Fig. 4.

3.3.1. Dream report data—overall differences

Since the percentage of imagery reports, the average number of visualizable nouns, and the average visual imagery ratings could be considered as three separate measures of the single concept of dream imagery, a 2 × 2 repeated measures MANOVA was conducted, treating each of these three measures as dependent variables. No significant main effect was found for Condition (Nicotine vs. Placebo) $F(3,11)=1.55, p=0.26$. However, a significant main effect for Sleep Stage (REM vs. Stage 2), $F(3,11)=3.60, p<0.05$, and Interaction (Condition ×

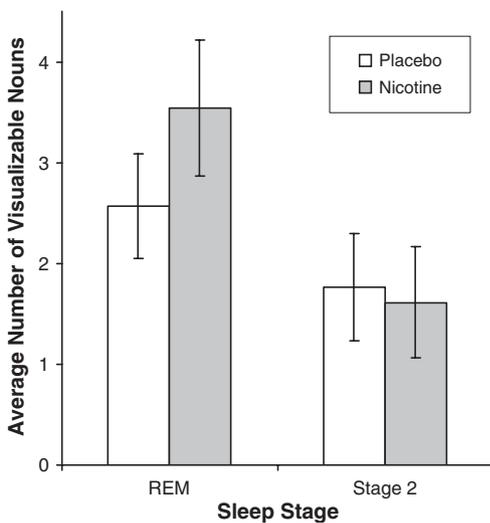


Fig. 3. The average number of visualizable nouns (nouns of objects that can be seen as in waking life) as judged by an independent rater (blind to conditions), in mentation reports from Stage 2 Nicotine, Stage 2 Placebo Control, REM Nicotine and REM Placebo Control conditions. Error bars represent standard error (S.E.) of the mean.

Sleep Stage) $F(3,11)=6.08, p<0.02$, was found. This result suggests a general difference in imagery measures between REM and Stage 2 sleep, and differences in imagery between Nicotine and Placebo only within REM sleep. In order to allow further interpretation of these statistical findings, separate 2 × 2 repeated measures ANOVAs were then conducted using each of the three imagery measures, which are presented in the following sections.

3.3.2. Dream report data—average percentage of imagery reports

For average percentage of imagery reports (Fig. 2), a 2 × 2 repeated measures ANOVA showed no significant main effects for Condition (Nicotine vs. Placebo) $F(1,13)=3.74, p=0.08$. A significant effect for Sleep Stage (REM vs. Stage 2) $F(1,13)=11.06, p<0.01$; and Interaction (Condition × Sleep Stage) $F(1,13)=5.17, p<0.05$, was observed. This result shows a significant difference in percentage of imagery reports between REM and Stage 2 sleep and a difference in the percentage of imagery reports between Nicotine and Placebo within REM sleep.

3.3.3. Dream report data—average number of visualizable nouns

For average number of Visualizable Nouns (Fig. 3), a 2 × 2 repeated measures ANOVA showed no significant main effect for Condition (Nicotine vs. Placebo) $F(1,13)=0.54, p=0.48$ or Interaction (Condition × Sleep Stage) $F(1,13)=1.50, p=0.24$. A significant main effect for Sleep Stage (REM vs. Stage 2) was observed, $F(1,13)=6.51, p<0.05$. This result suggests a general difference in imagery measures between REM and Stage 2 sleep, but no differences in imagery between Nicotine and Placebo Conditions.

3.3.4. Dream report data—average imagery ratings

For the average Imagery Ratings (Fig. 4), a 2×2 repeated measures ANOVA showed no significant main effect for Condition (Nicotine vs. Placebo) $F(1,13)=1.80$, $p=0.20$. A significant effect for Sleep Stage (REM vs. Stage 2) $F(1,13)=5.63$, $p<0.05$; and Interaction (Condition \times Sleep Stage) $F(1,13)=20.13$, $p<0.001$, was observed. This result shows a significant difference in average Imagery Ratings between REM and Stage 2 sleep and a difference in average Imagery Ratings between Nicotine and Placebo within REM sleep.

4. Discussion

4.1. Sleep architecture

This study attempted to determine the effect of 24-h transdermal nicotine patches on sleep architecture in smokers. It was hypothesised that participants would experience shorter sleep time and more arousals while using the transdermal nicotine patch compared to the placebo patch condition. Results suggested an arousing effect from the nicotine patches with a greater percentage of time awake in the nicotine condition and an increased mean number of micro-arousals. Consistent with previous findings [18], significantly less REM sleep time and significantly more arousals were observed in the nicotine patch condition compared to placebo control. Also, the proportion of sleep time that participants spent in NREM Stages 1 and 2 and SWS remained similar across the nights, suggesting nicotine effects quite specific to REM sleep and arousal [18].

4.2. Mentation reports

It was hypothesised that the mentation reports obtained from participants while wearing the transdermal nicotine patch, would include more visual imagery, be subjectively rated as more vivid, and contain more visualizable nouns than reports given while not wearing the patch. Although a general difference between Stage 2 and REM sleep reports was observed, no general difference between any of the mentation report measures was found between the Nicotine and Placebo nights. However, a significant interaction revealed a greater percentage of visual imagery reports, which were rated as more vivid, were given following REM awakenings on the nicotine night, compared to placebo control. NREM Stage 2 sleep showed little difference in mentation reports following awakenings from the nicotine condition compared to placebo control.

One participant in the current study experienced a nightmare while wearing the nicotine patch, which was so vivid and disturbing the experimenter had to enter the room to reassure her. A number of participants in the current study also reported remembering more interesting dreams following the experimental night that they would have liked the opportunity to report. Consistent with these observations, participants in Salin-Pascual and Drucker-Colin's [16] study reported having vivid dreams (some of which were classed as the "nightmares") while using the patch. In contrast, Gillin et al. [18]

found no increase in dreams, atypical dreams or nightmares after nicotine patch nights compared to placebo. However, one must remember that both of these studies collected reports the following morning from questionnaires and sleep logs. The current study implemented systematic sampling of dream reports specifically from REM and Stage 2 NREM sleep across the night.

The finding of a higher frequency of dream imagery, rated as more vivid, in the Nicotine condition compared to Placebo, but only within REM sleep, is difficult to interpret. If nicotine acted on PGO activity in humans as in animals, one would expect a decrease in the quality and quantity of mentation within REM sleep. However, the opposite was observed.

As the current study was conducted on humans, the effect of transdermal nicotine on PGO waves could not be directly measured and it is difficult to infer from the results what, if any, effects on PGO activity may have occurred. On the one hand, the average time spent in the REM sleep state was seen to decrease while wearing the nicotine patch, suggesting the suppression of REM sleep phenomena, including PGO waves. On the other hand, the mentation reports given following REM awakenings, while wearing the patch, were significantly more frequent and rated as significantly more vivid than REM mentation on the control night, which suggests stimulation of sleep mentation processes and thus REM processes and PGO waves.

It could be postulated that nicotine would down regulate PGO activity in our study based on Vazquez et al. [10] finding in cats that PGO spike activity was eliminated by the application of transdermal nicotine patches. However, it could be argued that this finding cannot be related to the current study as Vazquez et al. [10] used very strong nicotine patches of 17.5 mg, 35 mg and 52.5 mg on cats weighing between 2.5 and 3.5 kg, while the current study used patches of 14 mg or 21 mg on adult humans. The high doses of nicotine used by Vazquez et al. [10] produced severe side effects such as vomiting and profuse salivation in a number of animals and the results of using such high doses may not be comparable to the changes expected by the relatively low doses used in the current study. It may be that very large doses of nicotine are required in order to produce such inhibitory effects on REM PGO activity.

Another possible explanation is that nicotine does not act on PGO activity in the same way in humans as documented in cats. For example, there are several differences in PGO activity of the cat and rat [29]; so much so that the rat was initially believed to be absent of PGO activity [30]. Therefore, it could be that the nature of human PGO activity may differ from cats to the extent that nicotine does not produce the effects on humans that would be expected based on cat PGO physiology.

If one accepts that nicotine most likely affects PGO activity in cats and rats in the same way as humans (which is a fundamental premise of the AS and AIM models), one must then question the relationship between PGO activity and dream mentation in this study. The correspondence between the occurrence of PGO waves in the cat and characteristics of sleep mentation in humans has not always been consistent in previous research [31]. PGO activity is virtually absent during sleep

onset (SO) and at its lowest during SWS [32,33]. These are both periods of vivid visual hallucinations in the form of hypnagogic imagery [34] and sleep terrors [35]. Furthermore, Nielsen et al. [36] have shown that REM sleep restriction can subsequently enhance SO mentation, suggesting the presence of “covert REM” processes other than PGO activity. PGO activity is most intense in NREM for about one minute before REM sleep in the cat, however reported mental imagery is not enhanced from awakenings during these periods [37]. REM deprivation experiments with cats show that PGO activity increases in frequency in REM during rebound. Increases also occur in NREM during the deprivation procedure [38]. Again however, reported mental imagery is not enhanced from awakenings during these periods [37].

Within the limitations of the current study, the relationship between nicotine, PGO activity and dreaming cannot be resolved. However, a future method of measuring PGO activity in humans may help to determine the relationship between PGO waves, the action of nicotine and sleep mentation.

One final explanation for the results of the current study is that nicotine stimulates general RAS arousal, and this then stimulates an increased quality and frequency of mentation reports [22–24]. Cortical arousal has been implicated in dream production and EEG arousal has previously been linked to the reporting of mentation [39–41]. For example, sleep onset mentation occurs at times of high alpha activity [34], and REM sleep, where the higher proportion of mentation reports are found, shows very fast, wake-like EEG frequencies [28]. As participants in this current study showed significantly more awake time and micro-arousals while wearing the nicotine patch as compared to the control condition, it may be that the changes seen in the visual quality of reported mentation reports in REM sleep was associated with this higher activation. If this were the case however, it would be expected that the generalised arousal, caused by the nicotine would initiate a change to the mentation reports obtained from Stage 2 awakenings as well. However, no significant difference was found between the Stage 2 mentation reports between the experimental and control nights. Alternatively, one could speculate that the arousal produced from nicotine only showed detectable effects on mentation when combined with the elevated cortical arousal that normally occurs during REM sleep. Such an interpretation is consistent with arousal-based theories of dream recall [39–41].

4.3. Methodological considerations

When considering the placebo baseline dream report data, Dream Imagery % does appear higher from Stage 2 (47.6%) and lower from REM (67.9%) compared to previous studies using similar rating methods (e.g. [42]: Stage 2: 22.9–43.8%, REM: 93.3%; [43]: Stage 2: 17%, REM: 84%). However, it is well known that there is considerable variability in dream report frequency across individuals [14]. Apart from the current sample being smokers, the sample size and techniques employed were not considerably different from these previous studies to suggest poor sampling. It may simply be that the

sample in this study contained individuals whose NREM and REM dream reporting was more convergent than observed previously. The average waking time of conditions was not significantly different and was toward the early morning (approximately 3:30 am–4:30 am), where the characteristics of NREM and REM dreams become more convergent [44]. Such sample differences and variation between individuals is the reason why the present study, and those previously using such measures, have utilised repeated measures designs [14]. This allows for effective testing of statistical differences within the same individuals across treatment conditions, despite considerable variation between individuals. Therefore, consistent statistical differences in dream report frequency across treatment conditions within the same individuals, such as those found in this study, cannot be ignored.

In the human brain, many variables involved in the administration of a substance can alter the effect it has on cellular activity and brain systems [1]. Even a drug with specific activity may still produce nonspecific effects [45]. While the availability of nicotine patches has allowed the present non-invasive investigation into the effect of a cholinergic agonist on the sleep and dreams of humans, the dose was applied via indirect systemic transdermal delivery. Furthermore, this study investigated smokers who had varied smoking habits ranging from 6 to 30 cigarettes/day, and of different cigarette nicotine strengths and so possibly had different tolerances to the transdermal nicotine, although no effect of this kind was tested. Furthermore, the effects of nicotine patches on smokers may be problematic to extrapolate to non-smokers, as the pharmacokinetic and pharmacodynamic effects of transdermal nicotine differ between smokers and non-smokers [15,16].

4.4. Conclusions

Overall, the results of this study are consistent with three general conclusions. The application of transdermal nicotine patches in smokers initially results in:

1. *Increased sleep fragmentation*—with a high percentage of time awake and more ASDA micro-arousals.
2. *Less REM sleep*—with NREM sleep relatively unaffected
3. *Increased REM dream quality*—with a greater frequency of visual imagery reports and higher imagery ratings specifically from REM sleep. Combined with previous animal studies showing that transdermally delivered nicotine blocks PGO activity [10–12], the current results do not appear consistent with PGO-based hypotheses of dreaming, such as the Activation-Synthesis or Activation, Input and Modulation (AIM) models. [3].

References

- [1] Hobson JA. The dreaming brain: how the brain creates both the sense and the nonsense of dreams. USA: Basic Books; 1988.
- [2] Hobson JA, McCarley RW. The brain as a dream state generator: an activation-synthesis hypothesis of the dream process. *Am J Psychiatry* 1977;134:1335–48.

- [3] Hobson JA, Pace-Schott EF, Stickgold R. Dreaming and the brain: toward a cognitive neuroscience of conscious states. *Behav Brain Sci* 2000; 23:793–842.
- [4] Solms M. Dreaming and REM sleep are controlled by different brain mechanisms. In: Pace-Schott E, Solms M, Blagrove M, Harnad S, editors. *Sleep and dreaming*. Cambridge: Cambridge University Press; 2003.
- [5] Sitaram N, Wyatt RJ, Dawson S. REM sleep induction by physostigmine infusion during sleep. *Science* 1976;191:1281–3.
- [6] McCarley RW. Brainstem cholinergic systems and models of REM sleep production. In: Montplaisir J, Godbout R, editors. *Sleep and biological rhythms: basic mechanisms and applications to psychiatry*. New York: Oxford University Press; 1990. p. 131–47.
- [7] Siegel JM. REM Sleep. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*, 4th ed. PA: Elsevier Saunders; 2005.
- [8] Baghdoyan HA, Rodrigo-Angulo ML, McCarley RW, Hobson JA. A neuroanatomical gradient in the pontine tegmentum for the cholinergic induction of desynchronised sleep signs. *Brain Res* 1987;414:245–61.
- [9] Jewett RE, Norton S. Effects of some stimulants and depressant drugs on the sleep cycle of cats. *Exp Neuropsychol* 1966;15:463–74.
- [10] Vazquez J, Guzman-Marin R, Salin-Pascual RJ, Drucker-Colin R. Transdermal nicotine on sleep and PGO spiles. *Brain Res* 1996; 737:317–20.
- [11] Guzman-Marin R, Alam MN, Mihailescu S, Szymusiak R, McGinty D, Drucker-Colin R. Subcutaneous administration of nicotine changes dorsal raphe serotonergic neurons discharge rate during REM sleep. *Brain Res* 2001;888:321–5.
- [12] Mihailescu S, Guzman-Marin R, Drucker-Colin R. Nicotine stimulation of dorsal raphe neurons: effects on laterodorsal and pedunculopontine neurons. *Eur Neuropharmacol* 2001;11:359–66.
- [13] Lagrue G, Cormier S, Mainguy M, Rouillet-Volmi MC. Nicotine substitution therapy. *Sleep disorders and dreams*. *Presse Med* 1994;23 (19):908–9.
- [14] GlaxoSmithKline. Consumer Medical Information: Transdermal nicotine —NicabateCQ controlled release nicotine patch. <http://www.nicabatecq.com.au/CQPatches/cmi.html>.
- [15] Wetter DW, Fiore MC, Baker TB, Young TB. Tobacco withdrawal and nicotine replacement influence objective measure of sleep. *J Consult Clin Psychol* 1995;63(4):658–67.
- [16] Salin-Pascual RJ, Drucker-Colin R. A novel effect of nicotine on mood and sleep in major depression. *NeuroReport* 1998;9:57–60.
- [17] Transdermal Nicotine Study Group. Transdermal nicotine for smoking cessation. *JAMA* 1991;266:3133–8.
- [18] Gillin JC, Lardon M, Ruiz C, Golshan S, Salin-Pascual R. Dose-dependent effects of transdermal nicotine on early morning awakening and rapid eye movement sleep time in non-smoking normal volunteers. *J Clin Psychopharmacol* 1994;14(4):264–7.
- [19] Antrobus JS, Fein G, Jordan L, Ellman SJ, Arkin AM. Measurement and design in research on sleep reports. In: Ellman SJ, Antrobus JS, editors. *The mind in sleep: psychology and psychophysiology*. 2nd ed. New York: John Wiley & Sons, Inc; 1991. p. 83–121.
- [20] Srivastava ED, Russell MAH, Feyerebend C, Masterson JD, Rhodes J. Sensitivity and tolerance to nicotine in smokers and nonsmokers. *Psychopharmacology (Berl)* 1991;105:63–8.
- [21] Foulds J, Stapleton J, Feyerebend C, Vesey C, Jarvis M, Russell MAH. Effect of transdermal nicotine patches on cigarette smoking: a double blind crossover study. *Psychopharmacology (Berl)* 1992;106:421–7.
- [22] Steriade M. Arousal: revisiting the reticular activating system. *Science* 1996;272:225–6.
- [23] Steriade M. The corticothalamic system in sleep. *Front Biosci* 2003; 8:878–99.
- [24] Perry E, Walker M, Grace J, Perry R. Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends Neurosci* 1999;22 (6):273–80.
- [25] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of sleep stages human subjects. Los Angeles: Brain Information Service/Brain Research Institute UCLA; 1968.
- [26] Jasper HH. The ten–twenty electrode placement system of the International Federation. *Electroencephalogr Clin Neurophysiol* 1958; 10:495–501.
- [27] Roehrs T, Merlotti L, Petrucelli N, Stepanski E, Roth T. Experimental sleep fragmentation. *Sleep* 1994;17(5):438–43.
- [28] ASDA. EEG arousals: scoring rules and examples. A preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:174–84.
- [29] Datta S, Siwek DF, Patterson EH, Cipolloni PB. Localization of pontine PGO wave generation sites and their anatomical projections in the rat. *Synapse* 1998;30(4):409–23.
- [30] Stern WC, Forbes WB, Morgane PJ. Absence of ponto-geniculo-occipital (PGO) spikes in rats. *Physiol Behav* 1974;12(2):293–5.
- [31] Pivik RT. The psychophysiology of dreams. In: Kryger MH, Roth TR, Dement WC, editors. *Principles and practice of sleep medicine*. London: W.B. Saunders Company; 1994. p. 384–93.
- [32] Vogel GW, Barrowclough B, Giesler DD. Limited discriminability of REM and sleep onset reports and its psychiatric implications. *Arch Gen Psychiatry* 1972;26(5):449–55.
- [33] Brooks DC. Waves associated with eye movement in the awake and sleeping cat. *Electroencephalogr Clin Neurophysiol* 1968;24(6):532–41.
- [34] Vogel GW. Sleep-onset mentation. In: Ellman SJ, Antrobus JS, editors. *The mind in sleep: psychology and psychophysiology*. 2nd ed. New York: John Wiley & Sons, Inc; 1991. p. 125–42.
- [35] Broughton RJ. Parasomnias. In: Chokroverty S, editor. *Sleep disorders medicine: basic science, technical considerations and clinical aspects*. Newton (MA): Butterworth-Heinemann; 1995.
- [36] Nielsen T, Stenstrom P, Takeuchi T, Saucier S, Lara-Carrasco J, Solomonova E, et al. Partial REM-sleep deprivation increases the dream-like quality of mentation from REM sleep and sleep onset. *Sleep* 2005;28(9):1083–9.
- [37] Pivik RT, Halper C, Dement W. Phasic events and mentation during sleep. *Psychophysiology* 1969;6:215.
- [38] Ferguson J, Henriksen S, McGarr K, Belenky G, Mitchell G, Gonda W, et al. Phasic event deprivation in the cat. *Psychophysiology* 1968;5:238–9.
- [39] Antrobus J, Kondo T, Reinsel R, Fein G. Dreaming in the late morning: summation of REM and diurnal cortical activation. *Conscious Cogn* 1995;4:275–99.
- [40] Lehmann D, Koukkou M. All brain work—including recall—is state dependent. In: Pace-Schott EF, Solms M, Blagrove M, Harnad S, editors. *Sleep and dreaming: scientific advances and reconsiderations*. Cambridge, UK: Cambridge University Press; 2003.
- [41] Conduit R, Crewther S, Coleman G. Shedding old assumptions and consolidating what we know: toward an attention-based model of dreaming. In: Pace-Schott EF, Solms M, Blagrove M, Harnad S, editors. *Sleep and dreaming: scientific advances and reconsiderations*. Cambridge, UK: Cambridge University Press; 2003.
- [42] Conduit R, Bruck D, Coleman G. Induction of visual imagery during NREM sleep. *Sleep* 1997;20:948–56.
- [43] Conduit R, Crewther S, Coleman G. Spontaneous eyelid movements during sleep are related to dream recall on awakening. *J Sleep Res* 2004; 13:137–44.
- [44] Fosse R, Stickgold R, Hobson JA. Thinking and hallucinating: reciprocal changes in sleep. *Psychophysiology* 2004;41(2):298–305.
- [45] Gaillard JM, Nicholson AN, Pascoe PA. In: Kryger MH, Roth TR, Dement WC, editors. *Principles and practice of sleep medicine*. Philadelphia: W.B. Saunders Company; 1994. p. 338–48.