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Nicotine facilitates memory consolidation in perceptual learning

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ABSTRACT

Perceptual learning is a special type of non-declarative learning that involves experience-dependent plasticity in sensory cortices. The cholinergic system is known to modulate declarative learning. In particular, reduced levels or efficacy of the neurotransmitter acetylcholine were found to facilitate declarative memory consolidation. However, little is known about the role of the cholinergic system in memory consolidation of non-declarative learning. Here we compared two groups of non-smoking men who learned a visual texture discrimination task (TDT). One group received chewing tobacco containing nicotine for 1 h directly following the TDT training. The other group received a similar tasting control substance without nicotine. Electroencephalographic recordings during substance consumption showed reduced alpha activity and P300 latencies in the nicotine group compared to the control group. When re-tested on the TDT the following day, both groups responded more accurately and more rapidly than during training. These improvements were specific to the retinal location and orientation of the texture elements of the TDT suggesting that learning involved early visual cortex. A group comparison showed that learning effects were more pronounced in the nicotine group than in the control group. These findings suggest that oral consumption of nicotine enhances the efficacy of nicotinic acetylcholine receptors. Our findings further suggest that enhanced efficacy of the cholinergic system facilitates memory consolidation in perceptual learning (and possibly other types of non-declarative learning). In that regard acetylcholine seems to affect consolidation processes in perceptual learning in a different manner than in declarative learning. Alternatively, our findings might reflect dose-dependent cholinergic modulation of memory consolidation.

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1. Introduction

Repeated practice in a perceptual task such as a visual texture discrimination task (TDT) (Karni and Sagi, 1991, 1993) leads to a permanent and consistent change in the perception of the stimuli involved in this task. This special type of learning is known as 'perceptual learning' (PL) (Gibson, 1963). PL has been observed for various sensory modalities including visual (Karni and Sagi, 1991, 1993; Schoups et al., 1995), auditory (Bao et al., 2001; Schmidt-Wilcke et al., 2010), tactile (Bende and Nordin, 1997), and multisensory perception (Beer and Watanabe, 2009; Batson et al., 2011; Beer et al., 2011). PL impinges on many aspects of every-day life. For instance, PL shapes the auditory system of musicians to be more sensitive to the fine details of music (Bharucha, 1987) or it enhances the visual system of radiologists for the subtle malformations in medical images (Harley et al., 2009). PL is a special type of non-declarative learning. PL does not require voluntary control and does not even require awareness of the to-be-learned stimulus array (Watanabe et al., 2001). PL is specific to the trained stimulus configuration. For instance, PL effects in visual perception are specific to the trained retinal location, stimulus orientation, motion direction, spatial frequency, and the trained eye (Crist et al., 1997; Karni and Sagi, 1991; Schoups et al., 1995; Sowden et al., 2002; Watanabe et al., 2001, 2002). Single cell recordings in macaques showed that PL alters the orientation tuning of cells in the primary (V1) (Schoups et al., 2001) and extrastriate visual cortex (Yang and Maunsell, 2004;

Abbreviations: ACh, acetylcholine; AChR, ACh receptor; C-group, control group; EEG, electroencephalography; ERP, event-related potential; FFT, fast Fourier transformation; nAChR, nicotinic AChR; N-group, nicotine group; N1, N2, negative ERP components; P1, P2, positive ERP components; P300, positive EEG deflection with onset latency around 300 ms post stimulus onset; PL, perceptual learning; TDT, texture discrimination task; V1, primary visual cortex; VEP, visual ERP.

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Adab and Vogels, 2011). Brain imaging studies showed that PL modulates the blood-oxygenation-level-dependent (BOLD) response to visual stimuli in V1 of humans (Kourtzi et al., 2005; Yotsumoto et al., 2009; Schwartz et al., 2002; Sigman et al., 2005). More recently, electroencephalography (EEG) studies in humans showed that PL affects the amplitude of early visual event-related potentials (VEP) (Bao et al., 2010; Pourtois et al., 2008). These studies imply that PL primarily reflects plasticity in sensory cortices rather than other brain areas. As such it is distinct from other types of non-declarative learning such as procedural or emotional learning (Fahle and Poggio, 2002; Hawkey et al., 2004; Herry et al., 2010).

Memory consolidation in PL is facilitated by sleep (e.g., Aeschbach et al., 2008; Karni et al., 1994; Mednick et al., 2003; Yotsumoto et al., 2009; but see also Hussain et al., 2009). For instance, no learning effects were found on a PL task when participants were re-tested on the same day without a sleep period whereas reliable learning was found after a one-night sleep (Karni and Sagi, 1993; Yotsumoto et al., 2009) or even a 90 min day-time nap (Mednick et al., 2003). However, unlike declarative memory consolidation, which seems to be facilitated during slow-wave-sleep (SWS) phases (Rasch et al., 2007), consolidation in PL seems to be promoted by rapid-eye-movement (REM) sleep (Karni et al., 1994). Although the mechanisms for memory consolidation during sleep are still debated (Stickgold and Walker, 2005; Diekelmann and Born, 2010), it is now well accepted that the cholinergic system modulates the consolidation of memory (Hasselmo, 2006). For instance, SWS phases are characterized by a relative reduction of the neurotransmitter acetylcholine (ACh) in the hippocampus (Kametani and Kawamura, 1990; Marrosu et al., 1995). Hasselmo and McGaughy (Hasselmo and McGaughy, 2004; Hasselmo, 2006) proposed that this reduction in ACh levels during SWS suppresses afferent signals and enables excitatory cortical feedback that promote memory consolidation. Recent studies demonstrated that declarative memory consolidation is not only facilitated by blocking ACh receptors (AChR) during sleep (Gais and Born, 2004) but also during the post-learning phase in the awake state (Rasch et al., 2006). In contrast to declarative memory consolidation, little is known about the role of the cholinergic system during non-declarative memory consolidation – and in particular PL. A few studies reported enhanced learning when the level or efficacy of ACh is raised during learning, that is during the encoding stage (Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998). For instance, Rokem and colleagues (Rokem and Silver, 2010) found that donezepil – a cholinesterase inhibitor with a relatively long life-time of several days – enhanced PL of a motion discrimination task in humans. However, they administered donepezil before the perceptual training and it remains unclear whether raising the efficacy of ACh facilitated PL by enhancing attention during encoding (Ahissar and Hochstein, 1993; Disney et al., 2007; Herrero et al., 2008) or by promoting consolidation during the post-learning phase. As reported above, several studies demonstrated enhanced declarative memory consolidation by blocking AChR after a verbal learning task (Gais and Born, 2004; Rasch et al., 2006, 2009). These studies found no cholinergic effects on a non-declarative mirror-reading task that served as control. Noteworthy that in these studies the AChR blocker was administered with a delay of at least 30 min after the learning task. Animal studies showed that scopolamine – an antagonist of muscarinic AChR – caused relative amnesia in a fear-conditioning task (Quartermain and Leo, 1988). This animal study suggests that high levels of ACh – rather than low levels as for declarative learning – may be relevant for successful consolidation in non-declarative learning. Interestingly, this amnesia was only observed when scopolamine was administered directly after the learning phase but not when administered 3 h later.

The goal of the present study was to examine the role of the cholinergic system for memory consolidation in PL – a special type of non-declarative learning. In particular, we tested whether nicotine – an agonist of nicotinic AChR (nAChR) – facilitates PL. Nicotine is known to enhance attention (Disney et al., 2007; Herrero et al., 2008). In order to avoid the possibility that the attention-enhancing effect of nicotine affected learning, in the current study the substance was administered *after* the training. Moreover, nicotine has a half-life time of about 2 h, which is relatively brief compared to other substances that modulate the cholinergic system (Alireza et al., 2007; Aktories et al., 2009). In order to avoid the possibility that the attention-enhancing effect of nicotine affected our perceptual test results, the test was performed on a separate day (Day 2). PL was examined by a texture discrimination task (TDT). This task was chosen, because previous studies have shown that it induces plasticity in the visual cortex (Karni and Sagi, 1991; Yotsumoto et al., 2009; Schwartz et al., 2002), a brain area that is especially sensitive to cholinergic modulation (Bentley et al., 2004). We were interested in how nicotine affects learning. Based on findings in declarative learning the nAChR agonist nicotine should impede memory consolidation. However, PL substantially differs from declarative learning. Based on previous animal research on non-declarative learning, we expected that nicotine will facilitate memory consolidation in PL.

2. Materials and methods

2.1. Participants

Twenty non-smoking adult men with no history of neurologic or psychiatric disorder and normal or corrected-to-normal vision volunteered for this study. All but two were right-handed. Their mean age was 24.3 years (range from 20 to 29). Prior to the experiment all participants filled out a screening form on nicotine consumption and sleep habits. Ten participants reported that they never consumed any form of nicotine (e.g., by smoking or smokeless tobacco) throughout life. The other participants indicated that they had some experience with nicotine. Of these participants the last consumption was on average eight months ago. Only participants who did not consume any form of nicotine for at least one month prior to the study were included. This minimum abstinence period was chosen in order to avoid the possibility of a nicotine tolerance (Pietila et al., 1998). All participants reported normal sleep the night before and the night between Day 1 and 2 of the experiment. All participants gave written informed consent prior to the study. They were informed that they will receive either chewing tobacco or a nicotine-free tobacco surrogate, but they were not told which of the two substances they received prior or during the experiment. Although all participants were informed in detail about all procedures of the experiment, they were naive regarding the study hypothesis. All participants were compensated for their participation by 7 Euro per hour or experimental credit hours for their studies. The study was approved by the ethical board of the University of Regensburg.

2.2. Procedure

The participants were randomly assigned to one of two groups: nicotine (N-group) or control (C-group). They were not informed about their group assignment until the end of the experiment. The experiment consisted of two sessions which were conducted on two consecutive days (see Fig. 1a). In the first session (Day 1), they were trained on the TDT for about half an hour. Immediately following this TDT training, participants from both groups received a chewing substance for 1 h. One group received nicotine (N-group) and the other group received a control substance without nicotine (C-group). During substance administration, they were asked to perform a sequence of visual oddball tasks and simple visual detection tasks. As these tasks served to control for the P300 and EEG alpha activity (see below) an EEG was recorded throughout the session. Once completed they were asked to remove the substance from their mouth. In the second session (Day 2), they were tested on the TDT (without any substance).

2.3. Texture discrimination task (TDT)

The TDT is commonly used task for examining PL and was first described by Karni and Sagi (Karni and Sagi, 1991, 1993). In the TDT, observers had to discriminate a set of foreground elements from an array of background elements (Fig 1a). The texture consisted of an array (19 rows by 23 columns, separated by 1.3° visual angle) of oriented white lines (20 cd/m^2, .1° × .9° visual angle) on a black background (<1 cd/m^2). Within each cell of the (invisible) array, lines were randomly positioned.