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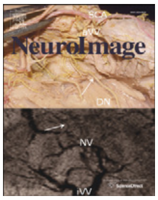

Sleep sharpens sensory stimulus coding in human visual cortex after fear conditioning

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ABSTRACT

Efficient perceptual identification of emotionally-relevant stimuli requires optimized neural coding. Because sleep contributes to neural plasticity mechanisms, we asked whether the perceptual representation of emotionally-relevant stimuli within sensory cortices is modified after a period of sleep. We show combined effects of sleep and aversive conditioning on subsequent discrimination of face identity information, with parallel plasticity in the amygdala and visual cortex. After one night of sleep (but neither immediately nor after an equal waking interval), a fear-conditioned face was better detected when morphed with another identity. This behavioral change was accompanied by increased selectivity of the amygdala and face-responsive fusiform regions. Overnight neural changes can thus sharpen the representation of threat-related stimuli in cortical sensory areas, in order to improve detection in impoverished or ambiguous situations. These findings reveal an important role of sleep in shaping cortical selectivity to emotionally-relevant cues and thus promoting adaptive responses to new dangers.

Introduction

One essential function of perception is to achieve efficient detection and discrimination of relevant information in the environment even when sensory cues are variable and incomplete. It is well established that sensory processing of emotionally-relevant stimuli is enhanced to allow rapid attention orienting and adapted responses to potential threats (Vuilleumier and Driver, 2007). However, how emotional learning induces long-lasting changes in sensory cortices in humans remains to be clarified. Animal studies have shown that pairing a stimulus with an aversive experience (e.g. electrical shock) through associative Pavlovian conditioning can subsequently shift the tuning curves of neurons in sensory cortices towards the characteristic sensory features of the conditioned stimulus and/or increase the number of neurons representing that stimulus (Gdalyahu et al., 2012; Resnik et al., 2011; Weinberger, 2004, 2007). Such remodeling of sensory representations may critically depend on modulatory signals from the amygdala (Armony et al., 1997; Chavez et al., 2009; Duvarci et al., 2009; Shaban et al., 2006). Likewise, in humans, Li et al. (2008) showed that initially indistinguishable odors (mirror-image molecules) can be transformed into discriminable percepts after aversive conditioning, associated with distinctive activations in the olfactory cortex as demonstrated by functional Magnetic Resonance Imaging (fMRI). Other studies in humans suggest that emotional relevance enhances perceptual processing in sensory cortices via feedback from the amygdala (Rotshtein et al., 2010; Vuilleumier et al., 2001, 2004), and also promotes long-term retention of emotional memories through a modulation of hippocampal systems (LaBar and Cabeza, 2006; Phelps, 2006). However, a role for the amygdala in mediating the effects of emotion on sensory plasticity and cortical selectivity in humans has not been demonstrated.

Recently, evidence has accumulated to show that neural changes underlying the consolidation of perceptual or emotional memories benefit from sleep (Diekelmann and Born, 2010; Maquet, 2001; Stickgold and Walker, 2013). For example, long-lasting improvement in perceptual learning tasks requires (rapid eye movement (REM) and non-rapid eye movement (NREM)) sleep and involves plasticity in early sensory cortices (Aeschbach et al., 2008; Gais et al., 2000; Schwartz et al., 2002; Stickgold et al., 2000; Yotsumoto et al., 2009). Similarly, emotional memories, fear conditioning, and extinction of a conditioned response

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are consolidated by a period of sleep following initial exposure (Baran et al., 2012; Payne and Kensinger, 2011; Sterpenich et al., 2007, 2009), particularly REM sleep (Menz et al., 2013; Nishida et al., 2009; Pace-Schott et al., 2009; Wagner et al., 2001). However, it is unknown whether sleep contributes to the remodeling of sensory representations of emotionally-relevant stimuli in sensory cortices, enhancing their perceptual discriminability subsequent to emotional learning.

Here, we hypothesized that fear learning modifies the perceptual sensitivity of sensory areas to discriminative stimulus features and is consolidated during sleep. This mechanism would allow the formation of a stronger, fine-tuned representation of fear-conditioned stimuli in cortical perceptual systems, possibly through offline reprocessing during sleep (Stickgold and Walker, 2013). Using fMRI, we tested this hypothesis by having human volunteers perform a discrimination task on morphed photographs of faces (Rotshtein et al., 2005), before and after one of the faces was associated with an aversive sound (see Methods). To assess the conjoint effects of emotion and sleep, face discrimination was tested again after a 12-h delay containing either one normal day of wakefulness or one night of sleep in two different groups of participants. Our results show that aversive conditioning enhanced the detection of the conditioned face in morphed stimuli, i.e., based on reduced visual information. Critically, such perceptual improvement only emerged after one night of sleep, and implicated selective changes in face-responsive brain regions. These data demonstrate that sleep contributes to the sharpening of neural representations of emotionally-relevant stimuli in sensory cortices, improving their subsequent perceptual discriminability.

Methods

General experimental design

The study consisted of two experimental parts separated by a 12-h time interval and participants were randomly assigned to either a Sleep ($n = 16$) or a Wake group ($n = 16$, Fig. 1A). During a minimum of 4 days preceding the experiment, all participants followed a constant sleep schedule (23:00–07:00 or 24:00–08:00 ± 30 min). Compliance to the schedule was assessed using a sleep diary and wrist actigraphy (Actiwatch, Cambridge Neuroscience, Cambridge, UK). Because we aimed at minimizing any experimental stressors (see Results section), the participants from the Sleep group slept in familiar conditions at their home with actimetry (but no EEG) (Hu et al., 2006; Payne et al., 2008).

For the first experimental part, subjects from the Sleep group came to the lab at 20:30 or at 21:30 whereas those from the Wake group came at 08:30 or 09:30. After an assessment of their subjective vigilance state (Karolinska Sleepiness Scale, KSS: 10-point visual analogue scale from 1: very sleepy to 10: very alert) (Akerstedt and Gillberg, 1990) and a 5-min computerized psychomotor vigilance task (PVT; Cajochen et al., 2004; Dinges and Powell, 1985), participants were scanned while they performed the face discrimination task (Baseline; see details below), followed by a conditioning session, during which one face was aversively conditioned. After the conditioning, the participants completed a second session of the face discrimination task (Test 1, similar to Baseline) to test for any immediate effect of the aversive conditioning on the face discrimination task. A short conditioning session was included at the end of the first experimental part in the MRI.

To test for the effect of sleep, the face discrimination task was administered again after a 12-h delay, with or without an intervening night of sleep. Thus, after the first experimental part, participants from the Sleep group slept at their home; sleep was assessed via questionnaires (The St. Mary's Hospital Sleep Questionnaire) (Ellis et al., 1981) and actimetry. Participants from the Wake group were allowed to go about their normal daily activities during the waking interval; they were instructed to avoid intense cognitive or physical activity, and not to sleep during the day, which was confirmed by questionnaires and actimetry. All participants came back 12 h later for the second experimental part, during which they again performed the discrimination task (Test 2), using the same experimental protocol and conditions as before. This second fMRI session aimed to assess any behavioral and neural effects of the aversive conditioning (by comparing trials with or without the conditioned face) and of sleep (by comparing the groups) on face discrimination thresholds, and any interaction of both factors. In total, the participants performed the face discrimination task three times: before (Baseline) and immediately after (Test 1) one face was conditioned, and after a 12-h consolidation period (either with or without sleep; Test 2). All sessions of the face discrimination task (20 min each), the conditioning task (12 min for the conditioning task and 2.5 min for the mini-conditioning task) and the face localizer (5 min) were performed in the MRI. During the first session (before the 12 h period of sleep or wake), participants stayed about 1 h in the MRI and during the second session (after the 12 h period) participants stayed about 45 min in the MRI.

Population

Thirty-two healthy participants (16 women and 16 men, mean age ± SD: 21.2 ± 3.6 years) participated in this study. A semi-structured interview established the absence of neurological, psychiatric, or sleep disorders. All participants were non-smokers, moderate caffeine consumers, and did not take any medication. They were not depressed as assessed by the Beck Depression Inventory (Steer et al., 1997), and had low to moderate anxiety levels as assessed by the Beck Anxiety Inventory and the STAI-T (Spielberger, 1983). Extreme morning and evening types were excluded (Horne and Ostberg, 1976). None of the participants complained of excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale (Johns, 1991) or of sleep disturbances as determined by the Pittsburgh Sleep Quality Index Questionnaire (Buysse et al., 1989). All participants were right-handed as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were randomly assigned to either a Sleep group ($n = 16$, 8 females, age 22.4 ± 4.0 [mean ± SD]) or a Wake group ($n = 16$, 8 females, age 20.0 ± 2.6). The groups did not differ in age or self-assessment questionnaire responses, including depression, anxiety, sleepiness, sleep quality and circadian rhythms (t-tests, all $p > 0.05$). All participants gave their written informed consent to take part in this study and received a financial compensation for their participation. The study was approved by the Ethics Committee of the Geneva University Hospitals.

Stimuli and tasks

Stimuli

We selected five photographs of female faces with a neutral expression, which were clearly identifiable as five distinct individuals (Fig. 1B). We then applied a linear morphing procedure to generate 15 equidistant steps or linear 'morphs' between each possible pair of original faces (Morpheus Photo Morpher, www.morpheussoftware.net). Scrambled, low-pass versions of these pictures were generated using dedicated Matlab (R2009b, MathWorks Inc., Sherbom, MA) scripts and served as visual masks.

Face discrimination task

During the face discrimination task, two face stimuli were presented in a rapid succession, always including one original face and the same face morphed with another face, and participants judged whether the two faces depicted the same or different individuals (Fig. 1C). In total, 5 distinct original identities were used, all unfamiliar to the participants (Fig. 1B). We expected that participants would respond 'same' on trials where both faces were close in morphing distance, thus sharing a high proportion of visual features; whereas participants should judge as 'different' those trials where the morphed face contained more visual