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Aversive learning increases sensory detection sensitivity

Fredrik Åhs[a], Stacie S. Miller[b], Amy R. Gordon[b,c], Johan N. Lundström[b,c,d,*]

[a] Center for Cognitive Neuroscience, Duke University, 203 Research Drive, 27708 Durham, NC, United States
[b] Monell Chemical Senses Center, 3500 Market Street, 19104 Philadelphia, PA, United States
[c] Dept. of Clinical Neuroscience, Karolinska Institute, Fogdevreten 2a, 17177 Stockholm, Sweden
[d] Dept. of Psychology, University of Pennsylvania, 3720 Walnut Street, 19104 Philadelphia, PA, United States

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ABSTRACT

Increased sensitivity to specific cues in the environment is common in anxiety disorders. This increase in sensory processing can emerge through attention processes that enhance discrimination of a cue from other cues as well as through augmented senses that reduce the absolute intensity of sensory stimulation needed for detection. Whereas it has been established that aversive conditioning can enhance odor quality discrimination, it is not known whether it also changes the absolute threshold at which an odor can be detected. In two separate experiments, we paired one odor of an indistinguishable odor pair with an aversive outcome using a classical conditioning paradigm. Ability to discriminate and to detect the paired odor was assessed before and after conditioning. The results demonstrate that aversive conditioning increases absolute sensory sensitivity to a predictive odor cue in an odor-specific manner, rendering the conditioned odor detectable at a significantly lower (20%) absolute concentration. As animal research has found long-lasting change in behavior and neural signaling resulting from conditioning, absolute threshold was also tested eight weeks later. Detection threshold had returned to baseline level at the eight week follow-up session suggesting that the change in detection threshold was mediated by a transient reorganization. Taken together, we can for the first time demonstrate that increasing the biological salience of a stimulus augments the individual's absolute sensitivity in a stimulus-specific manner outside conscious awareness. These findings provide a unique framework for understanding sensory mechanisms in anxiety disorders as well as further our understanding of mechanisms underlying classical conditioning.

1. Introduction

The perception of sensory cues can change according to their ecological significance. For example, if a the smell of gasoline has predicted a traumatic event, such as a blast, not only will this smell bring back emotions and bodily responses associated with the event, but the smell will also be more accurately distinguished from other smells (Croy et al., 2010; Vermetten and Bremner, 2003). In other words, a cue that predicts an aversive event can shape both behaviors and perception of the cue itself. While the bulk of the human literature on aversive learning has focused on behavioral plasticity, only a few studies have investigated changes in the percept of the cue that predicts the aversive event. However, many clinical problems, including anxiety disorders, depression, and chronic pain, are associated with altered sensory processing (Eldar et al., 2010). Thus, a precise understanding of how aversive experiences shape perception could advance knowledge about these common non-communicable disorders.

Alterations in how a cue is perceived following conditioning can be due to processes relating to attention as well as to processes at a more basic, perceptual level. A visual cue that has been paired with shock can capture spatial attention (Armony and Dolan, 2002), a process which is thought to depend on the amygdala (Zald, 2003). As such, attention can function as a filter for the plethora of sensory information that reaches the brain every second, letting through information with ecological significance. However, animal research, as well as human neuroimaging studies, also supports altered processing of conditioned cues at the level of the sensory cortices (Gdalyahu et al., 2012; Jones et al., 2008; Weinberger et al., 1993). The increased ability to discriminate cues following conditioning could be either a function of shifts in attention or of augmented sensory processing. Dissociating these mechanisms is a known problem. Nonetheless, the olfactory system might be especially well-suited for studying plastic changes due to the high degree of natural inter-subject variability in non-clinical olfactory performance (Cain and Gent, 1991), a variability which is considerably greater

* Corresponding author at: Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, United States. Tel.: +1 267 519 4690.
E-mail address: jlundstrom@monell.org (J.N. Lundström).

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in comparison to the visual and auditory systems (Gescheider, 1985).

To isolate the effect of conditioning on the sensory processing of conditioned cues from the effect of attention, a recent neuroimaging study used an elegant approach where two indistinguishable odors were used as conditioned stimuli and control stimuli (Li et al., 2008). Li et al. found different activation patterns in the piriform cortex, the so-called primary olfactory cortex, between the odor that was paired with shock and the unpaired odor even though participants did not posit explicit knowledge about which odor had been paired with shock. On the other hand, in a forced choice discrimination test, they could pick out the odor that had served as conditioned stimuli more often than would be expected by chance. This suggests that sensory conditioning might be specifically mediated by sensory augmentation rather than attention modulation mechanisms; Li et al. (2008) hypothesized that this sensory augmentation manifested behaviorally as a shift in the odor quality of the paired odor. However, more recent animal data have conclusively demonstrated that aversive conditioning induces learning-dependent anatomical and neuronal changes already in the olfactory bulb, the very first stage of neural processing of odors, and have also provided tentative evidence that these changes are accompanied by an increase in odorant-specific neurons in the olfactory epithelium (Doucette et al., 2011; Gdalyahu et al., 2012; Jones et al., 2008). Taken together, the aversive learning-induced plasticity shown already at the initial stages of olfactory sensory processing suggests that the demonstrated sensory augmentation is mediated by a shift in absolute sensitivity rather than discriminatory performance per se. This effect would manifest itself in an increased ability to detect the conditioned stimulus, a mechanism with significant survival value for the organism that might also serve as a route for clinical interventions.

We tested the hypothesis that aversive learning can increase an organism's absolute sensitivity toward a conditioned olfactory stimulus rather than merely modulating how a conditioned stimulus is perceived in relation to other stimuli. In Experiment 1, we sought to replicate the aforementioned study by Li et al. (2008) by presenting participants with two indistinguishable odorants (enantiomers), of which one was paired with shock (CSpaired) and one was not (CSonly). Following aversive conditioning, participants discriminated the odorant that had been paired with the aversive stimulus (CSpaired) from its enantiomer (CSonly). In Experiment 2, using the same odorant set as in Experiment 1, absolute detection threshold for a target odorant paired with an aversive stimulus (CSpaired) was assessed before and after aversive conditioning whereas thresholds for the same odorant were measured in a control group for whom an unrelated odorant served as CSpaired. We hypothesized that aversive conditioning would augment odor sensitivity to the target odorant for individuals who experienced the target odorant paired with shock but not for individuals who experienced shock paired with a different odorant. Finally, to assess whether demonstrated effects were mediated by a stable or transient reorganization, we assessed potential long-term plastic effects of aversive conditioning on odor sensitivity by testing odor detection threshold of the CSpaired odor eight weeks after the initial conditioning session.

2. Experiment 1—replicating the effect of aversive conditioning on odor discrimination

2.1. Materials and methods

2.1.1. Participants

Twenty participants (12 women) with a mean age of 24 (SD 4.75) participated in Experiment 1 after providing informed written consent. All participants were in good general physical and mental health. None were currently taking any form of medication, suffering from any form of hormonal, neurological, or autoimmune diseases, active smokers, and none had ever suffered a head trauma leading to unconsciousness; all variables known to affect olfactory processing. Participants were instructed not to eat or drink anything but water and not to chew gum during one hour prior to testing as well as not to wear any perfume or scented products on the day of testing. Smokers were not included in the study. None of the participating women used oral contraceptives, and all were tested within the first five days of the menstrual cycle to limit the impact of potential menstrual cycle effects (Lundstrom et al., 2006a). All aspects of the study were performed in accord with the Declaration of Helsinki on Biomedical Studies Involving Human Subjects and approved by the University of Pennsylvania's Institutional Review Board.

2.1.2. Odor stimuli and delivery

Four odorants, two enantiomer pairs (structural mirror images), were used as stimuli: S-(+)-2-butanol (Sigma–Aldrich, CAS 4221-99-2), R-(-)-2-butanol (Sigma–Aldrich, CAS 14898-79-4), (+)-rose oxide (Fisher Scientific, CAS 16409-43-1), and (−)-rose oxide (Sigma–Aldrich, CAS 16409-43-1). These two enantiomer pairs were used because it has been repeatedly demonstrated that humans under normal circumstances are unable to discriminate between the respective enantiomer odorants when matched for intensity differences (Laska and Teubner, 1999; Li et al., 2008). In an initial pilot study ($n = 10$; 5 women), we determined clearly suprathreshold concentrations of the odorants that were deemed, by ratings on visual analog scales (VAS), to be iso-intense by statistical assessment using a repeated measures ANOVA (rm-ANOVA), $F(3,54) = .95$, $p > .42$. Separate Student's t-tests post hoc demonstrated that there were no differences between the four odorants (all p ns). Based on these measures, we diluted the odorants to the following concentrations (v/v) in 1,2-propandiol: 3% S-(+)-2-butanol (+BUT), 4.4% R-(-)-2-butanol (−BUT), 11.1% (+)-rose oxide (+ROSE), and 8.3% (−)-rose oxide (−ROSE). Please note that the negative and positive signs associated with the odor labels indicate intrinsic properties of these chiral molecules and are used here to distinguish the enantiomers; the signs do not symbolize CS+ or CS− status, which we have marked CSpaired and CSonly, respectively. Odors were always presented intranasally with a custom-built, computer-automated olfactometer capable of delivering odors in a temporally precise square-shaped form. The olfactometer was controlled by psychophysiological recording equipment (PsyLab7; Contact Precision Instruments, London, UK), which also handled the delivery of a 60 Hz constant current electric shock stimulation. Shock stimuli were delivered via two cup electrodes (Ag–AgCl) placed on the right forearm. The olfactometer design was based on an olfactometer previously described in detail (see, Lundstrom et al., 2010). To prevent irritation of the nasal mucosa over time, we used a low flow rate of 3.0 L/m (1.5 L/m per nostril), and air was directed to the nose only when the odor was delivered. Using a photoionization detector (PID), the mean onset-time and 10/90% rise-time of the odor stimuli were measured at 102 ms and 97 ms, respectively (Lundstrom et al., 2010). To allow for odor presentation non-synchronous with breathing, participants performed the technique of velopharyngeal closure during experimental blocks containing odor presentation (Kobal, 1981; Lundstrom et al., 2006b). This technique restricts nasal breathing and direct participants to breathe solely via their mouth.

2.1.3. Odor discrimination

Ability to discriminate between the two odors within each enantiomer pair was assessed pre-conditioning using a three-alternative, forced-choice (3AFC) discrimination test with nine repetitions within each enantiomer pair using +BUT and +ROSE always as target odorants and their enantiomer partner, −BUT or −ROSE, always as the two lure odorants. Each stimulus was presented for 2 s, including an auditory cue to participants to sniff, with 6 s in-between each presentation within each triplet and 30 s in-between triplets (see Supplementary Fig. 1 for experimental overview). Ability to discriminate between the two enantiomers of each pair was once again assessed post-conditioning using identical methods as described above for the discrimination test.

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2012.11.004.

2.1.4. Aversive conditioning

Prior to the aversive conditioning paradigm there was a habituation phase in which all four odors were presented three times, each, for 2 s (a total of 12 two-second presentations) in a pseudorandomized order to avoid potential effects of individual differences in familiarity with the odors. Pseudorandomization was used to prevent odors from being consecutively presented. No shocks were delivered during the habituation phase. To force the participants to focus on the odor and to assess potential differences in odor intensity, a verbal rating of odor intensity was collected on an 11-grade scale ranging from 0 (no odor) to 10 (very strong odor) after each odor presentation. An acquisition phase followed in which half of the participants received a shock following +BUT presentation (Group 1) and the other half received a shock following +ROSE presentation (Group 2). This division of participants was done to control for odorant-specific effects. Each conditioned stimulus (CSpaired, i.e., +BUT or +ROSE, for Group 1 and 2 respectively) always co-terminated with a 300 ms electric shock, whereas its enantiomer sibling (CSonly; i.e.-BUT or -ROSE) was never paired with a shock. A total of eight presentations of each odorant were given in a pseudorandomized order with an average inter stimulus interval of 20 s (±4 s). The intensity of the shock stimulus was individually determined by ratings on a visual analog scale (VAS) ranging from "feel nothing" to "very intense"