results in specific enhancement of the stimulated but not unstimulated input, indicating that LTP is homosynaptic.

What mechanisms underlie these developmental changes in LTP? Tao et al. provide intriguing evidence that the localization of the postsynaptic calcium response to TBS changes over development. TBS elicits a transient calcium elevation that is global in tectal neurons early in development (stage 40) but more focal in the dendritic tree of cells at a later stage (stage 44). These findings pose important questions. Do increases in cytosolic calcium activate a diffusible messenger that conveys heterosynaptic modification, or does calcium act alone? Do changes in the intrinsic membrane properties of these cells play a role in heterosynaptic LTP? Are there developmental changes in heterosynaptic LTD? Future experiments that dissect the relationship between calcium localization and the specificity of LTP will help answer these questions.

Although LTP has been shown to lack synapse specificity in other parts of the nervous system, this paper is the first to show that the same connections can be modulated through either heterosynaptic or homosynaptic LTP. In Tao et al., heterosynaptic LTP occurs only at the early developmental stage. Thus, the tool used to refine synaptic connections is itself refined over time. LTP and LTD crosstalk between synapses of different postsynaptic neurons as well as between synapses from different presynaptic neurons converging on a common postsynaptic cell have been described (Engert and Bonhoeffer, 1997; Fitzsimonds et al., 1997). These heterosynaptic modifications have been attributed to a variety of molecular mechanisms. Both extracellular diffusible messengers, such as nitric oxide and arachidonic acid, as well as cytoplasmic signaling mechanisms, including calcium and protein phosphatases, have been associated with LTP and LTD crosstalk (Malenka and Nicoll, 1999; Tao et al., 2001).

The changes in LTP specificity observed by Tao et al. seem to reflect specific requirements of the particular developmental stage. In the initial period after RGC axon terminals reach the tectum, afferent inputs must make connections within the target region. These connections are profuse and weak. The "sloppiness" of LTP during this period seems to allow for the uniform strengthening of redundant connections. One possible scenario is that heterosynaptic LTP is needed until the afferent inputs can, in some combination, drive the firing of the postsynaptic cell at a frequency that allows homosynaptic LTP to efficiently strengthen and refine active inputs.

It will be interesting to see whether changes in the specificity of LTP are a common theme during development. Although tadpole visual development has many parallels to that of mammals, there are distinct differences. At an early stage of development of the retinogeniculate synapse in mammals, retinal waves provide spontaneous synchronous activity of tens to hundreds of RGCs before eye opening (Feller, 1999). These waves may allow many weak, immature inputs to summate and drive the postsynaptic neuron, thus providing another remodeling mechanism for the stabilization of initial connections. However, unlike the tadpole tectum which receives only contralateral projections, the mammalian LGN receives afferent inputs from both eyes. Thus, retinal waves and LTP also contribute to a period of segregation of RCG axon arbors into eye-specific layers in the LGN (Katz and Shatz, 1996). Whether LTP is homosynaptic or heterosynaptic during this period is unclear. Notably, the properties of retinal waves are also modified during the course of development, further supporting the idea that some mechanisms of remodeling are inherently flexible and change with time to fit the job at hand. How heterosynaptic LTP is integrated with other mechanisms of synaptic remodeling may be revealed in future experiments.

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The Scented Brain: Pheromonal Responses in Humans

Using PET, Savic et al., in this issue of *Neuron*, found a sexually dimorphic neural response to two putative human pheromones. The specific regions activated combined with the pronounced sex difference depict a pheromonal-type brain response in humans. Here, we preview this finding and suggest that human pheromones exist.

In *The Man Who Mistook His Wife for a Hat*, Oliver Sacks (1985) describes Stephen, a medical student who, while under the influence of drugs, dreams of being a dog. He wakes up from this dream a radically different person: he is hyperolfactory. Stephen: "I woke to an infinitely redolent world—a world in which all other sensations, enhanced as they were, paled before smell." And later: "I went into the clinic, I sniffed like a dog, and in that

sniff recognized, before seeing them, the twenty patients who were there. Each had his own olfactory physiognomy, a smell-face, far more vivid and evocative, more redolent, than any sight-face."

Within a few weeks, Stephen lost his hyperolfactory sensitivity, presumably due to the transient nature of whatever drug-induced alteration occurred in his brain. Oddly, the cessation of this rather debilitating hyperolfactory condition was both a relief and a source of disappointment to Stephen, who longed for the sensory and emotional richness of his now lost olfactory world.

Combined with anecdotal medical reports of hyperolfactory reactivity following neural insult (Vuilleumier et al., 1997), this suggests either that brain damage gave rise to a new olfactory capability or that brain damage uncovered an olfactory capability that was previously inhibited or masked. The rapid onset of the enhanced olfactory function points to the latter. Could it be that humans live in a complex olfactory world, the awareness of which is constantly inhibited? Several lines of evidence suggest that humans indeed are constantly affected by and reacting to olfactory stimuli. Odors can affect behaviors ranging from the mundane, such as choice of seat in a waiting room, to the paramount, such as judgments of potential mate attractiveness (reviewed in Thornhill and Gangestad, 1999). Furthermore, undetected odors can alter mood and change patterns of brain activity as measured with EEG and fMRI (reviewed in Sobel et al., 1999).

Savic and colleagues (2001) used positron emission tomography (PET) to study the neural response to two odorants: 4,16-androstadien-3-one (AND) and oestra-1,3,5(10)16-tetraen-3-ol (EST). These steroidal compounds are synthesized after components present in human sweat and are considered putative human pheromones. Savic and colleagues found a striking sexually dimorphic response pattern to these compounds. EST induced activity primarily in the hypothalamic region of men but olfactory region of women. In contrast, AND induced activity primarily in the hypothalamic region of women but olfactory region of men (although to a lesser degree). This unparalleled sex difference in response to a chemosensory stimulus may be considered classically pheromonal in nature. Thus, these findings fuel what is perhaps the hottest debate in the study of chemical senses: do human pheromones exist?

All animals use chemical signals to communicate messages ranging from attraction to aggression and territorial marking. Pheromones are a unique subset of chemical signals first defined by Karlson and Luscher (1959) as "substances which are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process." Dramatic examples of mammalian pheromonal responses abound. For instance, a pheromone from one individual can suppress or induce estrus, accelerate puberty, or block pregnancy in conspecifics (reviewed in Preti and Wysocki, 1999, and references therein).

Mammalian chemosignals are transduced via a number of distinct neural subsystems, including the nervus terminalis, septal organ, trigeminal nerve, gustatory system, main olfactory system, and accessory olfactory system. Rodent pheromones are transduced primarily but not exclusively in the vomeronasal organ (VNO), the sense organ of the accessory olfactory system. The VNO structure is a tube that is usually located along the ventral edge of the nasal septum, anteriorly to the olfactory epithelium. Sensory neurons traverse from the VNO to the accessory olfactory bulb, which projects to various, mainly limbic, regions in the brain. These include the amygdaloid complex, through which this system may directly affect behavior, and the hypothalamus, through which this system may regulate endocrine state. Considering the significance of pheromonal effects in other mammals, two exclusive yet related questions exist regarding humans: do human pheromonal effects exist, and is there a functional human accessory olfactory system and VNO? It is important to separate these questions, as pheromonal effects can be mediated via the main olfactory system. Thus, a functional VNO is not a prerequisite for human pheromonal effects.

The best example of pheromonal responses in humans is menstrual synchrony. In 1971, Martha McClintock first reported that the menstrual cycle of women with no previous social contact became synchronized in time following establishment of constant interaction, e.g., roommates in dorms. Russell et al. (1980) later showed that this effect may be achieved solely by wiping compounds from the underarms of "donor" women on to the upper lips of "recipient" women. Stern and McClintock (1998) later demonstrated that odorless compounds from the armpits of women in the late follicular phase of their menstrual cycles accelerated the preovulatory surge of luteinizing hormone (LH) of recipient women and shortened their menstrual cycles. Armpit compounds from the same donors collected later in the menstrual cycle (at ovulation) had the opposite effect: they delayed the LH surge of the recipients and lengthened their menstrual cycles. A similar VNO-mediated pheromonal effect occurs in rats.

Research on naturally occurring stimuli has been complemented by studies of responses to synthesized stimuli. Researchers affiliated with Pherin Pharmaceuticals have identified and synthesized a family of steroidal compounds that they have termed "vomeropherins." These compounds have induced sex-specific changes in body temperature, heart rate, respiration rate, electrodermal activity, EEG pattern, plasma levels of LH, and follicle-stimulating hormone, as well as mood alterations (reviewed in Grosser et al., 2000). The compounds used by Savic et al. are similar to those used by the Pherin group. AND, a derivative of testosterone, is present in human sweat at far higher concentration in men than in women. EST resembles naturally occurring estrogens more prevalent in women than in men.

The brain response pattern reported by Savic is very different from that seen with imaging of ordinary odorants. A robust hypothalamic response is seldom seen with ordinary odorants, and such an extreme sex difference is never seen with ordinary odorants. Considering that the hypothalamus mediates pheromonal effects and that sex specificity is a hallmark of pheromonal effects, Savic's groundbreaking work adds significant weight to the claim that these compounds are human pheromones. The following speculative functional interpretation of Savic's results is tempting: increased activ-

ity in the hypothalamus may indicate an endocrine response; increased activity in the olfactory regions may indicate a behavioral response. Thus, the dissociation in Savic's results may represent an hormonal response to the pheromone of the opposite sex (potential mate) but a behavioral response to the pheromone of the same sex (potential competitor).

In rodents, some pheromonal responses are negated following ablation of the VNO yet remain intact following ablations in the main olfactory system. Thus, the debate over human pheromones has been unnecessarily intertwined with the debate over the existence of a functional human VNO. Until recently, the very existence of a VNO pit in adult humans was disputed. Recent evidence from large samples, however, has revealed an identifiable VNO aperture and duct, ranging in pit diameter from 0.2 to 2 mm, in the majority of human adults (Garcia-Velasco and Mondragon, 1991). Thus, the remaining question is human VNO functionality. Against functionality: neither receptors, an enervating nerve, nor an accessory olfactory bulb (the primary target of VNO neurons) have been identified in humans (Trotier et al., 2000). In support of functionality: an evoked surface potential has been recorded at the VNO in response to stimulation with putative pheromones but not ordinary odorants (reviewed in Grosser et al., 2000). Thus, the question of human VNO functionality remains open (reviewed in Meredith, 2001).

The above findings largely satisfy the classic definition of pheromones: "Substances which are secreted to the outside by an individual" (in humans: sweat) "are received by a second individual of the same species, in which they release a specific reaction" (in humans: change in timing of ovulation and sex-specific changes in physiological measures, levels of hormones, and brain activity) "for example, a definite behavior or a developmental process." It is only this last component of the classic definition that has not been decidedly demonstrated in humans. That said, evidence does exist for behavioral responses to these compounds, and it is indeed unlikely that a compound that has been shown to change psychological, physiological, hormonal, and neural measures of function will not have a behavioral counterpart. This, along with the recent finding of genes for VNO-type receptors in humans (Rodriguez et al., 2000), lead us to conclude that the question of whether human pheromones exist has been answered. They do. It is now time to move on and ask how pheromones take effect in humans (i.e., is there a human accessory olfactory system and functional VNO) and how the human pheromonal responses may be involved in both healthy human behavior and, more interestingly, how this system may be involved in processes of disease.

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