composition of NF-κB proteins in Schwann cells *in vivo* and in cell culture, suggesting that the environment of the cells can affect expression of κB binding proteins and may therefore affect the responses of oligodendrocytes to NF-κB activation. Thus we need further molecular dissection of the NF-κB proteins expressed during myelination, and their regulation by signals from axons and other cells in their environment. This aim might be accomplished by selective elimination of single proteins of the NF-κB complex, for example with gene targeting or RNA interference.

The involvement of NF-κB in myelination raises several questions. What is the signal that normally activates NF-κB in Schwann cells to induce differentiation of Schwann cells and myelination of axons? Activation of receptors for several different factors produced by cells within the myelinating environment can stimulate myelination by Schwann cells and/or oligodendrocytes. Examples include the neurotrophin BDNF[5], TNF-α[6], transforming growth factor-β[7] and integrin receptor ligands[8]. Whereas much attention has focused on factors produced by axons[9], myelinating signals may also come from astrocytes, microglia and oligodendrocytes. The specific intracellular cascade that leads to activation of NF-κB during myelination is not known, but might involve phosphatidylinositol-3-kinase (PI3K) and Akt kinase, as these kinases are activated by myelinating stimuli, and inhibition of PI3K inhibits myelination[10].

The genes induced by NF-κB that encode proteins involved in the myelination process are not known. Among likely target genes are the transcription factors Oct-6, Krox-20 and desert hedgehog, each of which is upregulated early in the myelination process and may be a critical regulator of genes encoding the proteins that mediate myelination; indeed, Oct-6 null mice exhibit delayed myelination, and myelination fails completely in Krox-20 null mice[11]. Nickols *et al.*[2] provide evidence that Oct-6 can be induced by NF-κB, but it is not known whether Krox-20 and desert hedgehog are similarly responsive. NF-κB might also directly regulate expression of proteins that mediate myelination, including myelin basic protein, myelin-associated glycoprotein (MAG), immunoglobulin-superfamily proteins, and the neural adhesion molecules L1 and NCAM[12]. The present studies focused on the myelination of peripheral neurons by Schwann cells. It will therefore be important to establish whether NF-κB has the same critical roles in the differentiation of oligodendrocytes and the process of myelination in the CNS.

Finally, the new evidence linking NF-κB to myelination is of considerable importance for several areas of basic and clinical neuroscience. For example, it will be of interest to determine if NF-κB regulates developmental and regenerative myelination in an identical manner. Inflammatory cytokines, such as those produced by microglia and astrocytes during demyelination and remyelination, are potent inducers of NF-κB in a variety of cell types, including oligodendrocytes and Schwann cells. One might therefore expect that activated microglia and astrocytes could modulate the process of remyelination (**Fig. 1**). It will also be important to determine whether abnormalities in pathways upstream and/or downstream of NF-κB are involved in the pathogenesis of demyelinating diseases such as multiple sclerosis, and whether pharmacological modulation of NF-κB might be used to prevent demyelination and/or facilitate remyelination in such disorders.

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Nosing in on the emotional brain

Stephan Hamann

Emotions can be defined by their intensity and pleasantness. A new fMRI study reports that these two attributes are processed independently by different brain regions.

The rich, sweet smell of morning coffee puts you in pleasant spirits as the day begins. But as you open the milk to pour into the coffee, your nose suddenly wrinkles at its spoiled smell, and your mood changes instantly to disgust. Although strong pleasant and unpleasant emotions like these might seem to be complete opposites, a paper in this issue by Anderson *et al.*[1] reports striking similarities in the brain's response to pleasant and unpleasant emotions (**Fig. 1**). A key brain area for emotion, the amygdala, responded equally to pleasant and unpleasant odors, solely on the basis of emotional intensity. In contrast, a different emotion-related region, the orbitofrontal cortex, responded almost exclusively to the pleasantness or unpleasantness of the odors. This fascinating glimpse into how the brain organizes its response to emotional odors carries important implications for understanding how the brain processes emotion.

Emotions can be defined largely on the basis of two primary dimensions: intensity (level of arousal) and valence (degree of pleasantness or unpleasantness)[2,3]. For example, a snake might be highly arousing and highly unpleasant, whereas an apple might be only mildly arousing and mildly pleasant. Though simple, this model of emotion can account for an impressive variety of psychological and physiological emotion phenomena[2,3]. It has remained unclear, however, whether these two basic dimensions are reflected in how the brain processes emotion and

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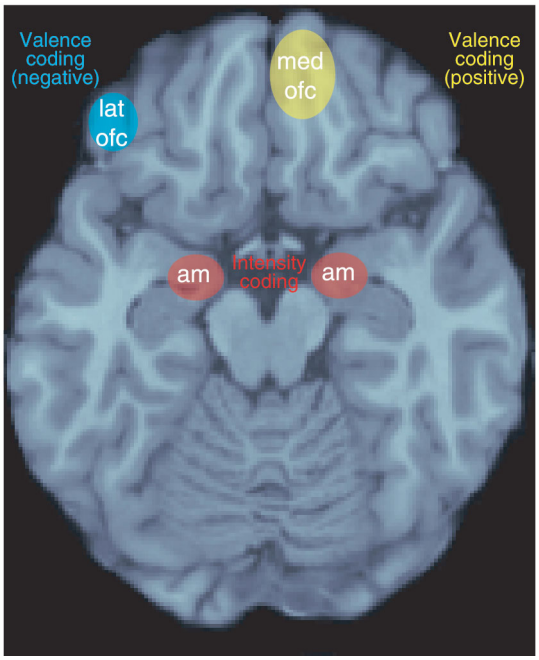

Fig. 1. Dissociable brain regions coding for intensity and valence of emotional reactions to odors. A summary of the primary regions activated in the study by Anderson *et al.*[1] and their functional roles in the processing of odor-elicited emotions. Activity in the bilateral amygdala (am, red) codes intensity, which is highly correlated with the strength of emotional response, independent of pleasantness. In contrast, activity in right medial orbitofrontal cortex (med ofc, yellow) codes for pleasantness but not intensity, and activity in left lateral orbitofrontal cortex (lat ofc, blue) codes for both unpleasantness and intensity.

how different brain regions contribute to this process. Although previous studies have hinted that the brain does indeed represent emotional stimuli according to these two dimensions[4,5], it has proven difficult experimentally to disentangle arousal from pleasantness. The reason for this lies with the tight linkage between arousal and pleasantness in the real world: highly pleasant and unpleasant stimuli also tend to be highly arousing. Furthermore, unpleasant stimuli generally tend to be more arousing than pleasant stimuli, likely reflecting the greater adaptive importance of avoiding potential harm versus stopping to smell the roses. In the unique domain of olfaction, however, emotional arousal can be manipulated independently from pleasantness, providing a means to independently vary these two stimulus dimensions while assessing the brain's responses.

In this issue, Anderson *et al.*[1] used olfactory stimuli to examine the neural organization of emotional responses by probing the brain's response to odors that varied in arousal and pleasantness. Subjects' brain activity was scanned using event-related fMRI while they took brief whiffs of odors at intervals. To vary valence, the authors used two odors: a pleasant, citrus-like odor and an unpleasant, rancid odor. The intensity and associated emotional arousal of each odor was manipulated by delivering either a low or high concentration of the odor to the subject. Pure air was used as a neutral baseline for comparison. To avoid expectancy effects, the odors and pure air were presented in an unpredictable order, and subjects were not asked to evaluate their emotional reactions but instead were simply asked to push a button indicating whether or not they detected an odor. After scanning, subjects were presented with the stimuli again and evaluated the arousal and pleasantness elicited by each odor.

The study focuses on activity in two regions, the amygdala and the orbitofrontal cortex, because of previous work linking these structures to emotion and olfactory processing. The primary finding was that arousal and pleasantness are processed independently, by different brain regions. The amygdala responded strongly to the emotional arousal elicited by the high-concentration, high-arousal odors, but did not differentiate between the pleasantness or unpleasantness of the odors. This arousal-dependent response fits nicely with similar arousal-dependent amygdala responses reported previously with visual emotional stimuli[5,6]. Conversely, a region in the right medial orbitofrontal cortex responded preferentially to pleasant stimuli regardless of arousal, whereas a region in left lateral orbitofrontal cortex responded preferentially to unpleasant stimuli. Critically, the amygdala responded more strongly to a high-intensity, pleasant odor than to a low-intensity, unpleasant odor, indicating that the amygdala was indeed responding to arousal level rather than to degree of pleasantness. These findings were corroborated by evidence that activity in these brain regions correlated highly with individual subject ratings of arousal and pleasantness. For example, subjects who reported higher arousal showed greater activity in the right amygdala, compared with subjects who reported lower arousal to the same stimuli, and conversely, activity in the right amygdala was not correlated with pleasantness ratings. In summary, brain responses to odors dissociated relatively cleanly along the two major dimensions of emotion.

Whether the functional segregation observed between the amygdala and orbitofrontal cortex in the present study holds outside the domain of olfaction remains an open question. The orbitofrontal cortex and amygdala have strong interconnections, and both regions receive direct projections from the primary olfactory cortex[7,8]. Emotions elicited in other sensory domains having different connectivity with the orbitofrontal cortex and amygdala may show a different pattern of functional segregation. Along these lines, although the current study focused on functional segregation, one would ultimately wish to know how the amygdala, orbitofrontal cortex and other brain regions interact dynamically during the processing of odors and other emotional stimuli to create a complete emotional experience. Analyses of dynamic functional connectivity between brain regions will become increasingly important in this regard, and have already identified potentially important interactions between the amygdala and the orbitofrontal cortex during aversive odor processing[8].

As the authors suggest, there may well be an important distinction between the neural basis of emotional responses elicited by sensory stimuli such as odors and tastes, and more complex, semantically rich stimuli such as visual scenes. For example, the pleasant emotional response triggered by receiving a bouquet of roses would require a sophisticated analysis of meaning and social information, whereas the pleasant fragrance

of a rose can be appreciated through a more direct chemosensory route. The rose's fragrance may trigger additional emotional reactions through associations, but these are not essential for an emotional response to occur. Given their differential origins, it seems reasonable to suppose that the organization of the brain's response in these two cases might also differ substantially.

The amygdala has often been portrayed as the center of fear and loathing in the brain, specialized to respond to highly aversive emotional stimuli. Indeed, considerable evidence supports this view. For example, direct electrical stimulation of the amygdala in humans can induce intense fear reactions, and intracranial recording of field potentials from patients with implanted amygdala electrodes shows increased activity while viewing unpleasant scenes but not pleasant or neutral scenes[9]. In addition, the amygdala has a well-established role in innate and learned fear responses, such as the classical conditioning of fear associations[10,11]. Against this background, it is surprising that in the present study the amygdala responded solely to the emotional intensity of odors, regardless of valence. There has been a growing recognition, however, that the amygdala has a more general role in adaptive reactions to a wide range of behaviorally salient stimuli, including pleasant and emotionally arousing visual stimuli such as erotica and appetizing food[6,12,13]. The work of Anderson *et al.*[1] supports this more general role for the amygdala by clearly showing that in the case of olfaction, the amygdala is not specialized for response to unpleasant emotion.

Overall, the evidence so far suggests that although the amygdala can respond to both pleasant and unpleasant emotional stimuli, it often is more responsive to unpleasant stimuli, for reasons that have yet to be determined. The current findings suggest that this greater role in negative emotion may be partly an illusion, however, induced by the correlation between unpleasantness and arousal. That is, even if the amygdala always responded solely on the basis of arousal (regardless of valence), its observed role in negative emotion would seem to be more prominent, simply by virtue of the higher emotional arousal triggered by unpleasant stimuli[14]. A more fundamental question concerns the degree to which the amygdala is intrinsically specialized or tuned toward negative emotion, after the greater arousal associated with negative emotion stimuli has been accounted for. The current study has shown that for olfaction, the amygdala has no intrinsic preference for negative emotion after the effects of arousal have been controlled. It will be intriguing to discover whether other domains of emotional stimuli will follow the lead of the nose.

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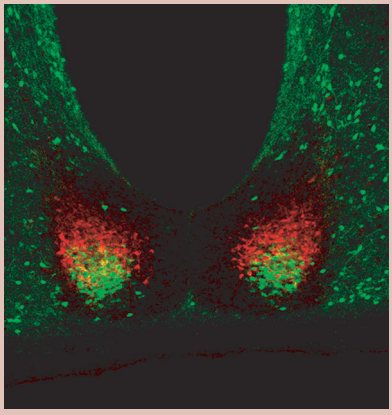
The master clock becomes a servant



In mammals, a specialized 'clock' or pacemaker in the hypothalamus called the suprachiasmatic nucleus (SCN) regulates daily rhythms in behavior and body function, such as sleeping and body temperature. Rhythms in the SCN are driven intrinsically, without external inputs, leading the SCN to be considered a master clock controlling other clocks within the body. However, this idea may be incomplete, report Michael Lehman and colleagues on page 111 of this issue. The researchers found that a rhythm in the phosphorylation state of the mitogen-activated protein kinase (MAPK) within a specific region of the SCN depended on external input from the eye. Therefore, at least in one case, the SCN may not be as in control as once believed.

The authors examined the SCN of hamsters with an antibody to the phosphorylated form of MAPK and found two rhythms: one located within the outer or shell region of the SCN, which peaked during the day, and another located within its core, which peaked during the night. The image shows phosphorylated MAPK expression (red) in the core partially overlapping with another SCN core marker, calbindin (green). In animals with both eyes removed, which leaves behavioral and physiological rhythms like locomotor activity and body temperature intact, the core pattern of phosphorylated MAPK was missing, whereas the shell pattern remained. Similar results were seen when both SCNs were removed and replaced by fetal SCN transplants, presumably because the transplants had not fully re-established afferent connections. Labeling the eye with an anterograde tracer revealed eye-specific terminals in close proximity to the core SCN cells that express phosphorylated MAPK, further supporting the hypothesis that these cells receive direct input from the eye. The loss in phosphorylated MAPK expression was also not a result of deafferentation-induced cell loss, because eye removal had no effect on cell density in the SCN core region.Now that it is apparent that at least one rhythm in the SCN depends on external input, the next step is to determine the functional significance of this eye-driven rhythm.

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