

# Perspectives on Neuroscience and Behavior

## Age, incremental training, and learning

The auditory localization pathway in the barn owl is an excellent model system for studying the neural mechanisms involved in experience-dependent plasticity. For the owl to localize a sound, the interaural timing differences and interaural level differences from the auditory stimulus are processed in parallel brain stem pathways that project to the central nucleus of the inferior colliculus. Spatial information is then conveyed to the exterior nucleus of the inferior colliculus where a spatial map is created and then conveyed to the optic tectum where it merges with a visual map of space (Knudsen 2002). Learning in this system has been studied by exposing owls to prismatic spectacles that produce a large horizontal shift in the visual field. When wearing prisms that produce a large shift (23 degrees), juvenile owls learn new associations between auditory cues and localization in visual space. This results in new maps of interaural time differences in the optic tectum. The prism experience induces the formation of learned circuitry in the external nucleus of the inferior colliculus in part through axonal sprouting and synaptogenesis. Juvenile owls can generate new maps following a single prismatic shift of 23 degrees, but adult owls cannot, suggest-

ing that experience-dependent plasticity is severely limited in adults. However, it has now been shown that if adult owls have incremental training with small shifts in prisms (6, 11, and 17 degrees), they are able to generate new maps where the degree of shift begins to approach that seen in juveniles (Linkenhoker and Knudsen 2002). In adult owls, once acquired, the new map can be reacquired with one large prismatic shift. These findings show that adults have a greater capacity for plasticity than previously recognized, and it emphasizes the importance of incremental training to develop this capacity. The value of incremental training has long been known both at the behavioral and physiologic levels, and the detailed neurobiologic knowledge of how this system operates in the barn owl will allow a better understanding of the mechanisms involved in experience-dependent plasticity.

Knudsen E. 2002. Instructed learning in the auditory localization pathway of the barn owl. *Nature* 417:322–8.

Linkenhoker B, Knudsen E. 2002. Incremental training increases the plasticity of the auditory space map in adult barn owls. *Nature* 419:293–6.

## Anxiety, neurosteroids, and the $\epsilon$ isozyme of protein kinase C

The lifetime prevalence of disorders involving anxiety can be as high as 25% in the United States, fortunately, however, increasingly effective pharmacologic and behavioral treatments are now available. Laboratory animal models of anxiety have demonstrated the central role of the gamma aminobutyric acid (GABA) neurotransmitter system in anxiety, and most drugs that treat anxiety affect the GABA or serotonin systems. Of the two principle subtypes of the GABA receptor complexes, the GABA<sub>A</sub> receptor is most relevant to anxiety, and its modulation by barbiturates, ethanol, benzodiazepines, and some neurosteroids results in anxiolysis, sleep, or anesthesia, depending on the dose used. Now it has been shown that mice lacking the  $\epsilon$  isozyme of protein kinase C (PKC $\epsilon$  null mice) have reduced anxiety-like behavior and reduced corticosterone and ACTH at baseline and in response to restraint stress (Hodge and others 2002). The PKC $\epsilon$  null mice also have an increased biochemical and behavioral sensitivity to neurosteroid modulators of GABA<sub>A</sub> receptors, and allopregnanolone (an allosteric activator of the GABA<sub>A</sub> receptor) lowered corticosterone levels in wild-type

but not PKC $\epsilon$  null mice. The GABA<sub>A</sub> antagonist bicuculline restored corticosterone and anxiety-like behavior in the null mice to wild-type levels, which suggests that the reduced anxiety-like behaviors and reduced corticosterone levels in the null mice are the consequence of enhanced GABA<sub>A</sub> receptor activity. The lack of a corticosterone reduction following allopregnanolone in the null mice is consistent with the idea that enhanced neurosteroid activation of GABA<sub>A</sub> receptors is a major factor reducing corticosterone levels in the null mice. These findings indicate that the  $\epsilon$  isozyme of PKC can now be a target for the development of new types of anxiolytic drugs and that methods to enhance the sensitivity to our own endogenous anxiolytic compounds could prove to be a fruitful area of new drug development.

Hodge CW, Raber J, McMahon T, Walter H, Sanchez-Perez AM, Olive MF, and others. 2002. Decreased anxiety-like behavior, reduced stress hormones, and neurosteroid supersensitivity in mice lacking protein kinase C $\epsilon$ . *J Clin Invest* 110:1003–10.

### Hippocampal volume and post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a constellation of distressing behavioral symptoms that appear in some individuals following exposure to actual or threatened injury or death to self or others. Symptoms can include recurrent distressing memories, thoughts, and dreams and physiological reactivity that can be spontaneous or triggered by external cues that resemble the original event. There are also symptoms of increased arousal and emotional numbing and avoidance of stimuli associated with the trauma. Laboratory animal studies have shown that severe and chronic stress can damage the hippocampus and that individuals with chronic unremitting PTSD have a smaller hippocampal volume as measured with structural MRI. Because only a portion of individuals exposed to the same trauma develop PTSD (the prevalence of PTSD in Vietnam combat veterans is 30%), it is not clear whether the reduced hippocampal volume is a consequence of the trauma exposure or is a preexisting condition related to increased symptom expression. Now there is robust data indicating that the smaller hippocampal volume found in individuals with chronic unremitting PTSD is a preexisting condition that predicts vulnerability to PTSD (Gilbertson and others 2002). MRI studies were conducted on 12 identical twins who had combat exposure and severe combat-related PTSD and on their 12 identical twin brothers who had no combat exposure and no PTSD. Controls were 23 identical twins with combat exposure and no PTSD and their 23 co-twins with no combat

exposure and no PTSD. There was no difference in the hippocampal volume between the individuals exposed to combat with PTSD and their unexposed twins without PTSD, and both groups had a smaller hippocampal volume than the control groups. There was a significant correlation between their own hippocampal volume and PTSD symptom severity in the exposed twins with PTSD ( $r \geq -0.64$ ), but more important, the hippocampal volume of the unexposed co-twin without PTSD also significantly correlated with the PTSD severity of their affected twin ( $r = -0.70$ ). Thus, the hippocampal volume of the twin unexposed to combat without PTSD predicted the PTSD severity of the exposed twin with PTSD as well as did the exposed twin's own hippocampal volume. This is compelling evidence that reduced hippocampal volume is a risk factor for developing PTSD rather than being a consequence of traumatic experience. Future studies of monozygotic and dizygotic twins will be able to distinguish the role of heredity versus shared environment as the cause of the reduced hippocampal volume, and this will aid our understanding of the role of reduced hippocampal volume in the pathogenesis of PTSD.

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. 2002. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience* 5:1242-7.

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