Gene tinkering makes memorable mice . . .

From the early days of genetic engineering, biologists and ethicists have debated whether the technique might one day allow parents to shape the intelligence and temperament of their children. Many scientists have argued that the hereditary underpinnings of these characteristics are so complex that such control falls in the realm of science fiction.

In the Sept. 2 NATURE, Joe Z. Tsien of Princeton University and his colleagues describe how the addition of a single gene endowed mice with superior memory and learning ability. "Our results suggest that genetic enhancement of mental and cognitive abilities such as intelligence and memory in mammals is feasible," the investigators conclude.

The improvement in mouse mental agility, without apparent side effects, stems from adding the gene for a protein that helps brain cells communicate. The study "demolishes the argument of those who claim that things like memory, learning, and intelligence are so complicated that scientists will never be able to figure out ways to enhance those traits," says Lee M. Silver, also of Princeton, who studies the social implications of genetic engineering.

Tsien's mice aren't the first engineered rodents with a super memory. Last year, Japanese researchers reported that some of their mice did unexpectedly well on certain memory tasks. The mutant mice were missing a protein that cells use to respond to the brain chemical called nociceptin. The absence of these receptors, however, impairs their hearing and some other brain functions.

Tsien's group created mice with extra copies of the gene for a component of the NMDA receptor, a protein complex on brain cells that responds to the neurotransmitter glutamate. The receptor seems suited to memory formation since it takes two closely timed but distinct stimuli at these complexes to make a nerve cell respond. This allows the brain to connect related stimuli, such as the striking of a match and the warmth of its flame, investigators speculate.

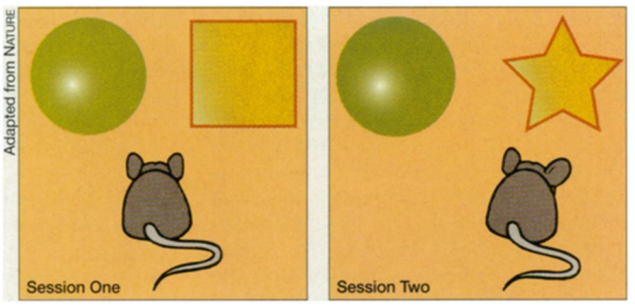
The NMDA receptor also plays a role in long-term potentiation (LTP), the strengthening of connections between nerve cells. Many scientists argue that the brain forms memories using LTP, though that hypothesis remains controversial.

The brain contains several NMDA-receptor types. The most active, so-called juvenile form declines in number as mice, and people, grow old. To counter that trend, Tsien's team made mice overproduce one subunit of the juvenile receptor.

Studies of brain cells of these transgenic mice revealed that they experience LTP much more readily than normal brain cells do. In addition, the transgenic mice scored better than normal mice on learning and memory tests. For example, the mutant mice better remembered the location of a platform submerged in a tank of milky water. The transgenic mice also learned more quickly to associate a foot shock with a sound.

Scientists caution that results in mice might not apply to people. "It's not at all clear that if you took a pill that improved memory in exactly the same way as [in] the mice, we would be any more intelligent," says Charles F. Stevens of the Salk Institute for Biological Studies in La Jolla, Calif. In fact, he says, an overactive memory might even interfere with intelligence.

If human genetic engineering becomes safe and practical, will people choose to boost the brain power of their children? "I do think it will be irresistible for future parents, but I don't think it will happen overnight," says Silver. Still, he notes that only recently he believed that genetic enhancement of intelligence was at least 25 years away. He now suspects that's a "conservative" estimate. *—J. Travis*



Compared with normal mice, the memory-enhanced mouse is more likely to explore a novel object (star) rather than one it encountered in a previous session.

. . . and hikes fear and anxiety in others

Since only a portion of the people exposed to traumatic events develop anxiety disorders, researchers suspect that some type of genetic vulnerability contributes to these distressing conditions.

Rodents may yield valuable clues to the presumably inherited roots of severe anxiety reactions, a new study suggests. Mice deprived of a gene that facilitates transmission of specific chemical messages in the brain represent a potential animal model of anxiety-prone people, reports a team of neuroscientists led by Florence Crestani and Hanns Mohler of the University of Zurich.

Experimental deletion of the mouse gene leads to a marked drop in the number of molecular receptors for a neurotransmitter known as GABA, the researchers contend. GABA dampens the activity of brain areas—such as the amygdala and hippocampus—implicated in fear and anxiety. Antianxiety drugs, such as Valium, work by activating the GABA receptors that Crestani and Mohler's group focused on.

An inherited shortage of these signal entry points into brain cells may predispose people to develop anxiety disorders in response to stressful or traumatic experiences, the scientists propose in the September NATURE NEUROSCIENCE.

They first examined brain slices taken from mice either retaining or missing a copy of the GABA-receptor gene. Those missing the gene had many fewer GABA receptors, mainly in the hippocampus, amygdala, and frontal brain.

Gene-deprived mice showed greater anxiety on several laboratory tests, the scientists say. For instance, in an elevated maze, they usually avoided walking along passages with no walls, unlike their DNA-intact comrades.

Receptor-poor mice also learned more quickly to react fearfully to a tone that regularly preceded a foot shock by 1 second, as well as to a light that occasionally appeared just before the tone and foot shock. This shows that, like anxiety-ridden humans, the genetically altered mice feel distressed even by events with a tenuous link to an actual threat, the scientists say.

Mutant mice performed as well on spatial learning tasks as receptor-rich mice did, indicating that the genetic loss influenced only anxiety. Moreover, the mutant mice became far less fearful after receiving injections of a Valium-like drug.

These mice "offer the promise of a genetic model of the anxiety-predisposed human," remark neurobiologist Stephan G. Anagnostaras of the University of California, Los Angeles and his colleagues in the same journal. Such mice may prove useful in testing new antianxiety drugs, they say.

Brain mechanisms by which the gene deletion pumps up anxiety remain uncertain, Anagnostaras' group notes.

Psychiatrist Kenneth S. Kendler of Virginia Commonwealth University in Richmond commends the new study as "beautiful work," although he says it's difficult to compare the mutant mice to people suffering from most anxiety disorders. The rodents, however, may help scientists understand the constant sense of anxiety and fright experienced by individuals diagnosed with generalized anxiety disorder, says Kendler.

—B. Bower