AMAZING PAPERS IN NEUROSCIENCE
Both Genetic and Environmental Changes Can Enhance Learning and Memory

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This review discusses two papers from the same lab that directly compared the effects of genetic enhancement with environmental enrichment on learning and memory in mice. In the first study mice were genetically manipulated to have an increased expression of the NR2B component of the NMDA receptor, associated with learning. These transgenic (Tg) mice showed greater current flow, larger EPSPs, and improved learning and memory on a variety of tasks. In the second experiment both the Tg mice and normal wild type (Wt) mice were raised in either a standard environment or given an enriched environment for two weeks. The differences in behavior and in receptor expression were compared among the four groups. The enriched Wt mice performed as well as both Tg groups on measures of fear conditioning. For the more difficult task of novel object recognition the enriched Wt mice performed as well as the Tg raised in a standard environment, but the enriched Tg mice performed significantly better than all other groups. Environmental enrichment caused an increase in receptor expression in both the Wt and Tg groups, but the Tg enriched mice had the highest expression levels. These papers clearly demonstrated that the mice's environmental enrichment caused behavioral differences for both Wt and Tg-enriched mice — with important implications for humans. They also raise questions about how a lab animal's environment might change its brain and/or behavior, with a potential impact on the results of studies using animals raised in impoverished conditions.

Key words: genetics; environment; learning; memory; nature and nurture.

There has long been debate between whether "nature" or "nurture," that is, genetics or the environment, control our behavior. Today there is a general recognition that both can play a role, since environmental and genetic manipulations alike have been shown to produce effects. It is hard to compare these directly, however, and impossible to do this for human beings. The two papers that are discussed here do, in fact, directly compare the effects, on mice, of a pure genetic manipulation and a simple environmental enrichment on both specific receptor levels and memory for newly learned tasks. The purpose of the first paper (Tang et al., 1999) was to show that a genetic enhancement of intelligence and memory is possible in mammals.

The authors chose to target the glutamate NMDA receptor (NMDAr). Presumably this was because glutamate, an excitatory neurotransmitter, has several different types of receptors that are known to be involved in learning and memory; of these, the NMDAr has received the most attention. The NMDAr itself has two components, NR1 and NR2; NR2 gates the NR1 channel. There are also two forms of NR2 in the forebrain, NR2A and NR2B. NR2B, which passes more current than NR2A, is normally down regulated during a rodent's transition from a juvenile to an adult. Tang et al. (1999) proposed that this down-regulation could explain the decreased memory performance seen in adult animals, including humans, as compared to neonates.

In order to test this idea, the lab postnatally over-expressed the NR2B receptor in the forebrains of wild-type (Wt) mice. The results showed that NR2B was present in the hippocampus, the amygdala, and the cortex of the transgenic mice (Tg), which were called "Doogie mice" after the precocious teenage star of the TV program "Doogie Howser, MD." Tang et al. (1999) examined the excitatory postsynaptic potentials (EPSPs), long-term potentiation (LTP), and various measures of memory. They found that the current through the NMDAr was virtually identical in the Wt and Tg mice up to 10 days of age. However, the current, which had fallen off in the Wt mice by day 18, stayed significantly higher in the Tg mice. Similar results were seen for LTP, where the Tg mice showed higher field EPSPs. The Tg mice also showed significantly better memory retention on all the behavioral tests that targeted those regions of the brain where NMDAr are found. These included novel object recognition (NOR), cued and contextual fear conditioning, and the Morris water maze (MWM). NOR depends on the hippocampus and the cortex, cued conditioning on the amygdala, and contextual conditioning on the amygdala and hippocampus. The MWM is a standard test of hippocampal function.

In NOR, animals are first presented with two identical objects and subsequently see one of the old objects, plus a new one. Mice explore objects by sniffing on them and, like other species, are attracted to the novel object. Thus, one would expect the mice to sniff more on the novel object, which assumes that they can remember having seen the other object in the past. Both groups performed equally well on day one, both sniffing significantly more on the novel object than the old one. However, the Tg mice sniffed significantly more on the new object for up to three days after the initial exposure, whereas the Wt mice had forgotten having seen the object by then. In fear conditioning, the mice were exposed to a shock paired with a tone in a specific cage and they froze to the shocks with both groups freezing equally. Later they were put back in the same cage without any tones and their freezing was observed (contextual conditioning). The Tg mice froze

more than the wild type at 1 hr, 1 day, and 10 days. Other groups of mice were subsequently presented with a tone in a different cage, and the Tg mice again froze more than the Wt at 1 hr, 1 day and 10 days (cued conditioning). Then extinction was examined. Twenty-four hours after the initial fear training, some animals were put back in the original cage (with no tone) a number of times. The Tg mice, which initially froze more than the Wt, stopped freezing more quickly than the Wt when both groups were repeatedly put back in the cage with no shocks (contextual extinction). Other groups were exposed to a series of tones 24 hours after training in a different cage with no shocks (cued extinction), and the same pattern of responses was seen: higher initial freezing followed by a faster drop off. These experiments indicate that the Tg mice normally remembered the place and the tone associated with the shock longer than the Wt, but they were also faster to extinguish when the place or cue were presented several times with no associated negative consequences.

Finally, the experimenters ran the MWM where animals must search in a pool of opaque water for a hidden platform. This task is a basic test of spatial memory and hippocampal function, which requires the NMDAr. The two sets of mice were similar in performance on day 1, but the Tg mice found the platform significantly faster on the third and fourth sessions, before the Wt mice caught up. Taken together, these experiments showed that genetically enhancing the NR2B receptor led to increased current flow through the NMDAr as well as enhanced learning, supporting the initial hypothesis that genetic enhancement could improve learning and memory, and also revealing a mechanism by which this could take place.

In the second experiment, Tang et al. (2001) again used both Wt and Tg mice, but now gave half of the mice an enriched environment for 2 weeks at age 3-5 months. The enriched environment was comprised of a large box with toys, tunnels, platforms, a wheel, pictures posted on the walls, and hidden chews; all of these elements were changed every two days. The enriched mice were in the box 3 hours per day continuously for 2 weeks. There were 3-4 mice per box, which was similar to their home environment. Thus there were four groups, Wt and Tg without enrichment, and Wt and Tg with enrichment. This design let the researchers compare the effect of environmental enrichment on certain behaviors, and on changes in the NR2B receptor, in the both the Wt and Tg mice. There was less of a focus on electrophysiology, but specific measurements were made of the expression level of four glutamate receptors: GluR1 (an AMPA receptor), NR1, NR2A, and NR2B.

The results were fascinating. Following environmental enrichment, the Wt animals improved significantly on cued and contextual fear acquisition and extinction (tested as described above), but the Tg mice showed no such improvement. Thus, the environmentally enriched Wt mice did as well as Tg mice with or without enrichment. The mice were also tested on novel object recognition (NOR), which was considered to be the most difficult task. With respect to NOR, both Wt and Tg mice showed improvement as a result of exposure to the enriched environment. Enrichment made the Wt mice perform as well as the Tg mice without enrichment, but not as well as the Tg mice with enrichment.

The behavioral results seen in the second paper (Tang et al., 2001) were consistent with the changes seen in the NMDAr as a result of environmental enrichment. The enriched Wt mice had a 250% increase in their NR2B receptors after 2 weeks, and showed smaller increases in the NR2A and Glur1 receptors. The Tg mice also had increases in the same three receptors. They had a similar increase in the NR2B receptors but they started from a higher base line, and also had a 300% increase in their NR2A receptors. The experiment thus showed that environmental enrichment led to a significant increase in the NR2B and other glutamate receptors following a rather brief enrichment period in both the Tg and Wt mice.

VALUE

These experiments were technically challenging and led to important findings. The first experiment showed that genetic enhancement influenced both brain function and behavior. In my opinion, however, the second experiment (Tang et al., 2001) is the more interesting, although it could not have been done without the first. As the authors point out, their study (Tang et al., 1999) is by no means the first to show that environmental enrichment influences both brain function and behavior. But, I do not believe that any other study has directly compared a genetic versus an environmental change in the same species, as the second study did (Tang et al., 2001). Nor has any other study so clearly shown that behavioral differences can be due as much to the environment as to genetics. This obviously has tremendous implications for the differences seen in human performance.

These findings also raise questions about how much the way that lab animals are housed can change both their brain and behavior. Most lab animals do not get any type of enrichment. How much this affects the validity of studies based on animals with impoverished brains and behaviors is an interesting question. In addition, the ways in which different labs house their animals could cause variations in both behavioral and genetic measures and may possibly explain some of the variation seen in experimental results.

AUDIENCE

The emphases of the two papers are rather different. The 1999 paper focuses heavily on electrophysiology, as well as on behavior. The intent there was to examine how increased NR2B expression changed the characteristics of the NMDA receptor, and there is a detailed discussion of how current flow, both normally and during LTP, is changed in the two cases. The 2001 paper has much less electrophysiology and simply states that genetically modified mice, which have an enhanced NMDA receptor, will be used as a comparison for the wild type mice. I have used these two papers in an advanced undergraduate / 1st-year graduate school class “Neuronal Bases of Learning and Memory,” but I think the second paper could

be taught as a stand-alone paper to anyone who had been introduced to the NMDA receptor. It could also be taught in more introductory and even general science classes.

Today, there is a far greater awareness than in the past that the nature/nurture question is not a case of "either/or," but that there is, instead, a strong influence of the environment on genetic expression. The 2001 paper shows this in a quantitative and unequivocal way that I find compelling.

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