nature neuroscience

A mouse's tale that grew in the telling

A recent paper in *Nature*, from a group led by Joe Tsien of Princeton University, described two strains of transgenic mice that showed enhanced performance in several memory tasks. This result, while undoubtedly interesting, would probably not have made headline news but for the authors' final conclusion: "Our results suggest that genetic enhancement of mental and cognitive attributes such as intelligence and memory in mammals is feasible." By raising the prospect of genetically enhancing human intelligence, the authors triggered a storm of worldwide media coverage, and while this has brought some welcome publicity to the field, their aggressive interpretation—both in the paper and in comments to the press—undoubtedly encouraged the sensationalizing of the study's implications.

To summarize the science first: the NMDA receptor (NMDAr) has been proposed to underlie the formation of associative memories. It is activated only when pre- and post-synaptic neurons fire together, and when this occurs, calcium enters the postsynaptic terminal; if the calcium influx is sufficient, it causes long-term potentiation (LTP) of the synapse. NMDArs are composed of several subunits, and during postnatal development the NR2B subunit is replaced by NR2A. The juvenile form of the receptor, with its longer opening time, admits more calcium than the adult form. This may explain why LTP is more readily induced in young animals than in adults, and (more speculatively) why young animals show greater behavioral plasticity. Tsien and colleagues therefore asked whether increasing expression of the NR2B subunit would lead to increased plasticity, and whether this would make it easier to form associative memories. Remarkably, the answer to both questions seem to be yes; the transgenic mice showed enhanced hippocampal LTP and enhanced performance on six different tests of memory and (possibly) learning. Although not all the effects can be attributed to the hippocampus, the results nevertheless strongly support the idea that NMDAr-dependent plasticity underlies the formation of associative memories.

It was not because of public interest in Hebbian plasticity, however, that the story became news, but rather because it raised two intensely controversial issues: gene therapy and the heritability of human intelligence. *The Washington Post* announced the findings with the headline "Scientists Add a Gene, and Intelligence Soars". The *New York Times* reported that Tsien "believes his work lays the basis for eventually doing the same in people". The cover of *Time Magazine* showed a baby staring (unusually thoughtfully) at a double helix, accompanied by a headline "The IQ Gene?" Meanwhile, bioethicists pontificated on the dangers of a 'designer baby' technology that only the rich could afford, the burden of raised expectations on the designer babies themselves, and the dilemma of whether genetically enhanced animals should be accorded enhanced rights.

Tsien now admits that he intended to provoke debate, and he certainly succeeded. Perhaps one should not begrudge the authors a little hyperbole in the heat of the moment; now that it has passed, however, some reflection seems in order.

First, have the authors really built a better mouse? The transgenic animals perform better in laboratory tests, and apparently have not yet shown any sign of deficits. But it is not clear that they would perform better in the real world. New memories may interfere with old ones, and it remains unknown whether lifelong memory capacity is enhanced in these animals. In any case, too much memory is not necessarily a good thing; for instance, the modified mice were also slower to forget their fears.

But even if these mice do have better memories, should they be labeled 'intelligent'? In most cases, they do not learn better than controls; they simply retain their memories longer (although they do show faster extinction of fear conditioning, which some consider a form of new learning). What, if anything, does this mean for humans? Although intelligence obviously requires memory, it is not clear that differences in human intelligence reflect differences in memory. (IQ has been reported to correlate with working memory, but this is a short-term form of memory with no known link to synaptic plasticity.) Tsien defines 'intelligence' as the ability to solve problems and argues that his mice meet the definition by showing enhanced performance on a watermaze; however, this seems more an accident of language than a scientific argument.

As for gene therapy to boost intelligence, to describe this as far-fetched would be an understatement. Attempts at gene therapy in other organs have been almost uniformly unsuccessful, but even if it were feasible, introducing genes into the brain of a healthy individual would seem indefensible, particularly given that no animal model could predict the cognitive effects. More plausible is the idea of developing drugs to up-regulate the endogenous NR2B gene or prolong the opening time of NR2A-containing receptors, as possible treatments for memory loss. Being reversible, however, these would not raise the same ethical dilemmas as gene therapy (and indeed a drug that prolongs the opening of AMPA receptors is already being tested in humans).

Perhaps the most serious issue arising from the study is the role of genes in human intelligence. This has long been a subject of debate, but most researchers these days agree that IQ score is at least partly heritable (which is not to say that it cannot be increased by intervention). If so, there must be genetic alleles that show associations with IQ. It is reasonable to ask whether NR2B might be among them, but there is no particular reason to think it will, and to refer to NR2B as "the IQ gene" is simply misleading. There is a serious discussion to be had about the social implications of discovering genes that affect human cognitive traits. Unfortunately, however, it didn't happen this time.