SPECTROSCOPY

The living brain, unlabeled

Researchers identify a biomarker for neural progenitor cells and use it to monitor these cells in the live brain.

Though it may sometimes seem unlikely that the human brain can generate new neurons—when a name irretrievably escapes you, for instance—neurogenesis does in fact continue, in a limited fashion, in adulthood. The cells that are responsible for this are the neural stem or progenitor cells (NPCs).

Methods to study these cells in the live brain are lacking. But in recent work, a large multidisciplinary group of researchers at the State University of New York, Stony Brook, the Brookhaven National Laboratory and the Cold Spring Harbor Laboratory, applied both chemical and clinical techniques to allow identification of unlabeled NPCs *in vivo*.

"Our hypothesis," explains Mirjana Maletic-Savatic, at Stony Brook, "was that NPC metabolism differs from other postmitotic cells in the brain, since these are the only dividing cells in the normal adult mammalian brain. So we searched for a metabolic marker of these progenitor cells, which would then enable us to detect them in the live human brain."

The researchers began by using proton NMR spectroscopy on isolated mouse samples to examine NPCs in comparison to neurons, astrocytes, oligodendrocytes and several other cell types that may be found in the brain. Somewhat surprisingly, they found that NPCs have a unique prominent peak (at 1.28 parts per million, or p.p.m.) that is not present in other cells. "We certainly expected that the whole metabolic fingerprint of progenitors would be different from, for instance, neurons," says Maletic-Savatic, "but we didn't think that one peak would stand out so much. In fact, in the beginning we couldn't believe it." But extensive *in vitro* experiments convinced the researchers that the 1.28 p.p.m. peak, suspected to be a mixture of lipids, is indeed a marker for NPCs, and the stage was set to use it for identification of the cells *in vivo*.

Magnetic resonance spectroscopy is the *in vivo* correlate of NMR spectroscopy, and can be used to provide information on metabolites in living tissue. However, the standard use of this technology is in the clinic and involves looking at a few abundant metabolites. In collaboration with Petar Djuric, also at Stony Brook, the researchers developed new algorithms based on singular value decomposition, a method that allows quantitative examination of a peak of known frequency even in a noisy background, which allowed them to detect the low-concentration 1.28 p.p.m. peak *in vivo*.

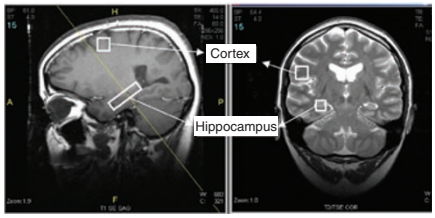

Figure 1 | Regions examined in the human brain. Boxes indicate the location of the cortex and hippocampus. Reprinted with permission from AAAS.

In rats as well as in humans (**Fig. 1**), they detected the marker in the hippocampus, a region known to harbor adult neurogenesis, but not in the cortex, where neurogenesis does not occur. Further, implanting exogenous NPCs into the rat brain or applying electroconvulsive shock, which is known to promote neurogenesis, produced a stronger 1.28 p.p.m. peak. Together, this provided support for the notion that the 1.28 p.p.m. marker does indeed mark NPCs.

Notably, when the researchers examined healthy humans of different ages, they saw a drastic drop in the 1.28 p.p.m. signal in 30-year-old adults as compared to children. As has been seen previously in animals therefore (and worriedly suspected by many adult humans), there is likely to be a substantial decline in neurogenesis in humans—with age.

"A really significant aspect of this work," Maletic-Savatic emphasizes, "is how many people with different expertise were involved." The collaboration allowed the researchers an unprecedented mixture of methodologies, with exciting future applications to the study of the diseased or degenerating brain.

Natalie de Souza

RESEARCH PAPERS
Manganas, L.N. *et al.* Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. *Science* **318**, 980–985 (2007).