600 ms of presentation of the test item were located more superiorly than those that differentiated accuracy more than a second after presentation. All changes in activity that related to the accuracy of verbal memory were recorded during the encoding phase with a similar pattern of earlier changes in more superiorly located neurons. The authors suggest that these temporal distinctions reflect an initial phase of processing related to the accuracy of perception, followed by a period of response monitoring.

Suzanne Farley

References and links

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FURTHER READING Ojemann, G. A., Schoenfeld-McNeill, J. & Corina, D. Anatomic subdivisions in human temporal cortical neuronal activity related to recent verbal memory. *Nature Neurosci.* 5, 64–71 (2002)

NEUROLOGICAL DISORDERS

Stimulating findings

Traumatic brain injury is a principal cause of fatalities and neurological or cognitive impairments in young people in Western society. It has long been thought that hyperactivation of *N*-methyl-D-aspartate (NMDA) receptors — excitatory receptors that are crucial for the formation of memories — underlies cognitive and neurological decline after head injury. Now, however, the teams of Biegón and Shohami challenge this assumption and show that loss of NMDA-receptor function might underlie these impairments.

Traumatic and ischaemic brain injuries trigger an increased release of excitatory neurotransmitters for ~30 min after head injury in animals, and for ~6 h to several days in humans. Delayed neuronal death and decline in function follow. Moreover, compounds that block NMDA receptors reduce cell death and improve outcome in animal models: this is most effective if the blockers are given less than 30–60 min after injury. But, surprisingly, clinical trials in humans that involved blocking NMDA receptors for several days after head injury have failed, and were actually associated with an increase in adverse effects.

So, might the duration of this NMDA-receptor hyperactivation in humans have been overestimated? This is the hypothesis that Biegón and Shohami tested.

They started by using autoradiography of a radiolabelled compound that blocks activated NMDA receptors (MK801) in a mouse model of

closed head injury: it turned out that NMDA hyperactivation was indeed short-lived (< 1 h) as shown by an increase in the density of MK801 binding. This might explain the short therapeutic window in animal models of traumatic brain injury. Intriguingly, a marked loss of function of NMDA receptors, which was longer lasting (> 7 days), followed this excessive stimulation.

The next step was to use NMDA to stimulate NMDA receptors at 24 and 48 h after traumatic brain injury. This significantly attenuated the neurological and cognitive deficits 2 weeks later. In support of this, NMDA blockers cancelled the beneficial effects of NMDA and led to a worsening of cognitive and neurological deficits.

This extended loss of NMDA-receptor function might therefore provide a therapeutic window for the treatment of cognitive and neurological deficits after head injury. The duration of this therapeutic window, however, needs to be determined in humans before clinical trials can take place. Once established, stimulation of NMDA receptors in the subacute post-injury phase might benefit brain-injured patients.

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Nature Reviews Genetics

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WEB SITES

Brookhaven Medical Department: <http://www.bnl.gov/medical/>
Hebrew University Faculty of Medicine: <http://medicine.huji.ac.il/>