Brain impairments have chiefly been linked to reduced brain activity. But recent UK research reveals that excessive brain activity can actually overwhelm the brain. Speaking at a symposium he chaired at the FENS Forum of Neuroscience today (9 July), Associate Professor Tobias Bast described studies demonstrating that intensified activity in two regions — the hippocampus and the prefrontal cortex — can impair memory and attention. This increased activity can be more detrimental than reduced activity or brain damage.

Describing his team’s work at the University of Nottingham, Dr Bast explained how deficient inhibitory transmission, resulting in abnormally raised activity in these brain regions, can disrupt memory and attention processing. This excess activity may contribute to memory and attention decline in patients with brain disorders like schizophrenia and Alzheimer's. The research findings may therefore offer new approaches to treating patients with these illnesses.

Within the brain, neurons ‘excite’ each other by sending out neurotransmitters, explained Dr Bast. This interaction, within a region and between regions, is kept under control by inhibitory signals. The key inhibitory neurotransmitter Gamma-aminobutyric acid, or GABA, restrains excess neural activity, preventing neurons from firing too much. In several studies, his team examined how ‘neural disinhibition,’ or deficient GABA transmission works.

“We’ve known for a while now that control by inhibition is important to maintain normal neural network activity,” he said. “But it wasn’t quite clear whether inhibition is actually required for cognitive functions — attention, memory, and so on.” Knowing that insufficient GABA transmission (disinhibition) has been connected to schizophrenia, Alzheimer’s, and other conditions involving cognitive decline, they investigated how impaired inhibitory transmission might affect these important cognitive functions. “We wanted to test whether neurons are too ‘trigger happy’ that would actually cause cognitive deficit.”

Their research focused on the prefrontal cortex and the hippocampus as areas important for memory and attention. The prefrontal cortex is critical in orchestrating complex cognitive functions, including mediating attention. The hippocampus is crucial in forming our everyday memory of events, including where and when they happened.

The team applied a drug specifically to these two brain areas in rats, blocking inhibitory GABA transmission in these two sections, thus increasing regional activity. Behavioural tests found that rats with deficient GABA transmission — and corresponding abnormally increased neural firing in these regions — performed poorly in memory and attention tasks.

The results confirmed that increased brain activity due to faulty inhibition disrupts some cognitive functions of the disinhibited regions, including prefrontal-dependant attention and hippocampus-dependant memory. Some functions that also require these regions were not as reliant on inhibitory neurotransmission and remained unaffected.
Additionally, researchers found that increased neural activity and faulty inhibition could have a more profound and widespread effect than just inhibiting a region, Dr Bast explained. The results showed that increased neural activity in the hippocampus not only disrupts some type of memory, which has long been known to require the hippocampus, as expected, but also impairs attention, which does not generally involve the hippocampus, but rather depends on the prefrontal cortex.

"So you find a somewhat paradoxical situation, that if you lesion an area, for example the hippocampus, attention is not affected. But if you stimulate it, suddenly attention is disrupted." This secondary finding reflects compelling connections between the hippocampus and the prefrontal cortex, he noted. "So increased activity might actually disrupt functions that don’t normally depend on the disinhibited region. Because of knock-on effects of one region on another, this can disrupt whole neural network.” He described his team’s ongoing work: “We are trying to really look at which networks are roped in when you have this disinhibition.”

With this new understanding, Dr Bast hopes continued research may lead to alternative approaches in treating patients with cognitive impairments resulting from brain disorders — including age-related cognitive decline, Alzheimer’s, and schizophrenia.

The memory and attentional impairments his team found are similar to those seen in human patients, he noted. “We make an effort to apply translational tasks that resemble tasks that can be used in humans. People suffering from certain cognitive disorders, such as schizophrenia or Alzheimer’s, when tested on these tasks, show similar impairments,” he said. “This facilitates translation of our findings to human cognitive disorders.”

Their results indicate that both too much and too little activity can cause impairments, and that memory and attention actually depend on balanced neural activity. "Evidence from cognitive disorders such as schizophrenia or Alzheimer’s finds that early on, there is too much activity in some areas, which may damage the brain; whereas later stages seem to be characterised by too little activity. There may be a relationship between the two, with the increased neuronal activity early in the disorder contributing to the neuronal damage characterising later stages. So if we can rebalance abnormal activity early on, it may restore attention and memory, and hopefully also prevent additional decline.”

Previously, attempts at cognitive enhancement and to treat memory and attention impairments mainly focused on ‘boosting’ brain activity, based on the fact that diminished activity or brain damage causes impairments in these functions. However, a re-think may be required, Associate Professor Bast explained. He noted that many drug companies, attempting to help patients with various cognitive impairments, have focused on compounds that dampen inhibitory transmission in memory and attention centres, to give the brain this ‘boost’. "But on the other hand, in many psychiatric disorders such as schizophrenia or neurological disorders such as early stages of Alzheimer’s, we now have evidence that there’s too little inhibition.” So he cautioned that such strategies may not improve, and may actually curtail these functions. Therefore, currently his team is exploring alternative compounds that might rebalance brain activity in these two areas, and to possibly even restore memory and attention.

END

Symposia S24: Cortical and hippocampal inhibitory GABA function in cognition and behaviour

Abstract: Cognitive deficits caused by prefrontal and hippocampal neural disinhibition

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The 11th FENS Forum of Neuroscience, the largest basic neuroscience meeting in Europe, organised by FENS and hosted by the German Neuroscience Society will attract more than 7,000 international delegates. The Federation of European Neuroscience Societies (FENS) was founded in 1998. With 43 neuroscience member societies across 33 European countries, FENS as an organisation represents 24,000 European neuroscientists with a mission to advance European neuroscience education and research. https://forum2018.fens.org/

Further Reading (Bast):

Hippocampal neural disinhibition causes attentional and memory deficits. T Bast, S McGarrity, R Mason, KC Fone, M Pezze. Cerebral Cortex 27. 2017, (9), 4447-4462. DOI: 10.1093/cercor/bhw247