Schizophrenia-related cognitive effects of hippocampal disinhibition: attentional and memory deficits

Stephanie McGarrity1,2, Kevin Fone3, Rob Mason3, Marie Pezze1,2 and Tobias Bast1,2

1School of Psychology, 2Neuroscience@Nottingham, 3School of Life Sciences
1lpxsm@nottingham.ac.uk

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1 – Functional significance of hippocampal disinhibition in schizophrenia

Hippocampal disinhibition has emerged as key feature of schizophrenia pathophysiology (Lisman et al., 2008; Schoedl et al., 2009; Hecker & Konradi, 2010). However, the role in symptom generation remains to be clarified.

The hippocampus is associated with rapid acquisition and use of everyday-type memory, such as place memory, and temporal to intermediate hippocampus can mediate diverse behavioral-control processes via functional connectivity to prefrontal and subcortical sites (Bast, 2011).

To test this hypothesis, we combined disinhibition of temporal to intermediate hippocampus by local microinfusion of the GABA-A receptor antagonist picrotoxin with behavioral and electrophysiological analyses in Lister hooded rats.

**Experimental strategy**

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**References**


2 – Locomotor hyperactivity

**Locomotor hyperactivity**

Locomotor hyperactivity may often reflect dopamine hyperfunction and, for this reason, has long been used as a simple psychosis-related behavioral index.

**Subconvulsive picrotoxin doses caused moderate locomotor hyperactivity.**

3 – Attentional deficits

**5-Choice-serial-reaction-time-task (5-CSRTT)**

The 5-CSRTT resembles continuous performance tasks used to test for attentional and executive deficits in schizophrenia patients and is dependent on prefrontal cortex (Chudasama & Robbins, 2006).

Hippocampal disinhibition disrupted prefrontal-dependent attention, as indicated by a selective reduction of correct responses (no other measures were affected).

**References**


4 – Memory deficits

**Delayed-matching-to-place (DMTP) watermaze test**

The watermaze DMTP task resembles the everyday memory task of using newly learned place and route memory, with which schizophrenia patients have marked problems (Al-Uzri et al., 2006).

**Waiting period**

The task is highly hippocampus-dependent, especially the search-preference measure (Bast et al., 2009; Pezze & Bast, 2012).

**Hippocampal disinhibition disrupted DMTP performance.**

5 – Picrotoxin induces neuronal disinhibition within temporal to intermediate hippocampus

**Electrophysiological recordings combined with hippocampal infusions**

Channel oscillations outside hippocampus were excluded from analysis.

**References**


6 – Conclusions

**Picrotoxin infusion increased neuron firing within temporal to intermediate hippocampus, consistent with neural disinhibition and mimicking hippocampal overactivity.**

Disinhibition of the temporal to intermediate hippocampus caused schizophrenia-related attentional and memory deficits, indicating a causal relation between hippocampal disinhibition and two key cognitive symptoms in schizophrenia. In addition, hippocampal disinhibition caused locomotor hyperactivity, consistent with psychosis-related dopamine hyperfunction.

Hippocampal disinhibition may, thus, be a key target for novel pharmacological treatment strategies, which may be tested using our rat model.