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**BACOPA MONNIERI (BRAHMI) CAN RECOVER AND PREVENT COGNITIVE DEFICIT IN SUB-CHRONIC PHENCYCLIDINE RAT MODEL OF SCHIZOPHRENIA BY ELEVATING VESICULAR GLUTAMATE TRANSPORTER TYPE 3 IN THE BRAIN**

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**Abstract**

**Background:** Glutamatergic hypofunction is implicated in schizophrenia. Reduced presynaptic glutamatergic markers, remarkably vesicular glutamate transporter type 1 (VGLUT1) and 2 (VGLUT2) indicates glutamatergic deficit leading to cognitive impairment in schizophrenia. However, few studies in VGLUT3 have been reported. Brahmi (Bacopa monnieri), a traditional herbal medicine, might be a new treatment and prevention for cognitive deficit in schizophrenia by changing cerebral VGLUT3 density.

**Objective:** To study cognitive enhancement- and neuroprotective effects of Brahmi on novel object recognition task and cerebral VGLUT3 immunodensity in sub-chronic phencyclidine (PCP) rat model of schizophrenia.

**Material and Method:** Cognitive enhancement effect study; rats were assigned to three groups; **Group-1:** Control, **Group-2:** PCP-administration, **Group-3:** PCP + Brahmi. Neuroprotective effect study; rats were assigned to three groups; **Group-1:** Control, **Group-2:** PCP-administration, **Group-3:** Brahmi + PCP. Discrimination ratio (DR) representing cognitive ability was obtained from novel object recognition task. VGLUT3 immunodensity was measured in prefrontal cortex, striatum and cornu ammonis fields 1-3 (CA1-3) of hippocampus using immunohistochemistry.

**Results:** DR was significantly reduced in PCP group compared with control. This occurred alongside VGLUT3 reduction in prefrontal cortex, striatum and CA1-3. PCP + Brahmi showed a higher DR score compared with PCP alone and this occurred alongside a significantly increased VGLUT3 immunodensity in prefrontal cortex and striatum. Brahmi + PCP group also showed a higher DR score compared with PCP alone and this occurred alongside a significantly increased VGLUT3 immunodensity in prefrontal cortex, striatum and CA1-3.

**Conclusion:** Reduced cerebral VGLUT3 produced cognitive deficit in rats receiving PCP. Interestingly, receiving Brahmi after PCP administration can restore this cognitive deficit by increasing VGLUT3 in prefrontal cortex and striatum. Receiving Brahmi before PCP administration can also prevent cognitive impairment by elevating VGLUT3 in prefrontal cortex, striatum and CA1-3. Therefore, Brahmi could be a new frontier of restoration and prevention of cognitive deficit in schizophrenia.

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**GPR52 agonists show pro-cognitive properties**

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**Abstract**

GPR52 is an orphan G protein-coupled receptor which is mainly expressed in the brain and shows a unique co-expression profile. In the striatum it is expressed almost exclusively in neurons also expressing D2-like dopamine receptors, whereas in the cortex it mainly co-expresses with the D1-like dopamine receptor. Because GPR52 is Gs-coupled, this has led to the prediction that agonists of GPR52 may have both antipsychotic and pro-cognitive properties by their action in the striatum and the prefrontal cortex, respectively. This makes GPR52 a particularly interesting target for the treatment of schizophrenia. While tool compounds have, indeed, been shown to reverse pharmacologically induced striatal hyperdopaminergic states, direct evidence for their efficacy in cognition was lacking. Here, we show data from in vitro, ex vivo and in vivo studies strongly supporting the hypothesized pro-cognitive efficacy.

Tool compounds were synthesized following Takeda patents WO2010/018874, WO2011/093352 and WO2012/020738 and their activity was confirmed in stably transfected HEK cells. The compounds led to a robust increase of intracellular cAMP concentrations, with an EC50 of 30 nM for the tool compound chosen for further characterization. To test the hypothesis that this increase in cAMP affects synaptic transmission in the prefrontal cortex, layer V responses to layer II stimulation were measured in prefrontal cortical rat brain slices. Bath application of the tool compound led to a robust and sustained increase in excitatory post-synaptic potentials, suggesting the possibility of pro-cognitive efficacy. To test this, working memory performance was measured in mice in the T-maze spontaneous alternation task. The deficit induced by the NMDA receptor antagonist MK-801 was dose-dependently reversed by the administration of the GPR52 tool compound agonist.

Together, these data show that GPR52 agonists also have potential for treatment of cognitive symptoms in psychiatric disorders characterized by cortical dopaminergic or glutamatergic hypofunction, such as schizophrenia.

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Evaluation of plasma and cerebrospinal fluid G72 protein levels and their correlations with psychiatric symptoms in schizophrenia and major depression

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**Abstract**

It has widely been accepted that D-serine plays a pivotal role in the regulation of glutamate neurotransmission as an endogenous co-agonist for the N-methyl-D-aspartate-type glutamate receptor (NMDAR). Consequently, the putative NMDAR dysregulation in the pathophysiology of schizophrenia and mood disorders could be due to disturbed D-serine signaling. Some studies described the changed D-serine levels in serum, plasma and cerebrospinal fluid (CSF) of patients with schizophrenia and major depressive disorder (MDD). Furthermore, G72 gene that
encodes an activator protein of D-amino acid oxidase (DAAO), a D-serine degrading enzyme, has been reported to associate with schizophrenia and bipolar disorders. To further elucidate the relationship between D-serine metabolism and psychiatric disorders, we presently examined by an ELISA technique the contents of G72 protein in plasma and CSF of Japanese patients with schizophrenia, MDD, and healthy controls. Neither plasma nor CSF G72 protein levels differ among the three diagnostic groups and relate with age of the participants in each group. These data do not support the previously observed distinct expression in plasma or CSF G72 protein levels in schizophrenia. On the other hand, we found a significant positive correlation between plasma G72 protein levels and the positive score ($r=0.027, p=0.43$) of the Positive and Negative Syndrome Scale (PANSS), but not the PANSS negative, general psychopathology or total scores, in the patients with schizophrenia. The CSF G72 protein levels did not significantly correlate with each of the four PANSS scores. In MDD, there was no significant association of either of plasma or CSF G72 levels with depression severity scores. To obtain an insight into the significance of the above correlation in schizophrenia, further studies to clarify the molecular and cellular mechanisms and extrinsic factors of the control of G72 expression are required.

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Differential changes on the white matter brain network in ultra-high risk for psychosis and first-episode psychosis
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Abstract

Background: Developmental process of dysconnectivity during transition into psychosis could appropriately be explored at the network level. However, no study has concurrently explored alterations in the white matter (WM) network of the brain among first-episode psychosis (FEP) and its prodromal stage.

Methods: Thirty-seven subjects with ultra-high risk for psychosis (UHR), 21 patients with FEP, and 37 healthy controls (HC) were recruited. 3-Tesla T1 structural and diffusion tensor images were reconstructed as weighted WM networks.

Results: At the global level, the UHR group showed a higher assortativity coefficient compared to the FEP group and a higher modularity Q compared to the HC group. At the local level, the FEP group showed a weaker left hippocampal-parahippocampal connectivity and a stronger left superior frontal-thalamic connectivity compared to the UHR and HC groups. More rightward asymmetry in the hippocampal-parahippocampal connectivities was seen in the FEP compared to the UHR and HC groups, and that asymmetry positively correlated with psychotic symptoms and negatively with level of functioning in the UHR group. Participation coefficient of the right pallidum increased in the FEP compared to the UHR and HC groups, and that measure positively correlated with nonspecific psychiatric symptoms in the FEP group.

Conclusions: UHR enhances function of WM network by increasing adaptivity and maintaining resilience without altering connection costs. Altered cortical-subcortical connectivity is weighted more than evidence late in time, compared to control. Under reduced E/I ratio, behavior is “indecisive”: the circuit exhibits weakened integration and reduced winner-take-all competition.

Our findings highlight the importance of cortical E/I balance in either direction can impair performance as assessed by psychometric functions. Nonetheless, these two regimes make dissociable predictions for the time course of evidence accumulation. Under elevated E/I ratio, behavior is “impulsive”: evidence early in time is weighted more than evidence late in time, compared to control. Under reduced E/I ratio, behavior is “indecisive”: the circuit exhibits weakened integration and reduced winner-take-all competition.

For working memory, we found disinhibition broadens the tuning of mnemonic, stimulus-selective persistent activity patterns; we tested this prediction using behavioral data from human subjects performing a spatial working memory task combined with ketamine infusion. The model further predicts increased behavioral variability degrading mnemonic precision, and impaired filtering of distractors. To test these predictions, we designed and tested behavioral tasks for patients with schizophrenia.

For decision making, we found disinhibition of E/I balance in either direction can impair performance as assessed by psychometric functions. Nonetheless, these two regimes make dissociable predictions for the time course of evidence accumulation. Under elevated E/I ratio, behavior is “impulsive”: evidence early in time is weighted more than evidence late in time, compared to control. Under reduced E/I ratio, behavior is “indecisive”: the circuit exhibits weakened integration and reduced winner-take-all competition.

Our findings highlight the importance of cortical E/I balance in cognitive functions. These models make specific predictions for behavior and neural activity that are testable in humans or animals under manipulation of E/I balance (e.g. via pharmacology) or in disease states.

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Cognitive control deficits in patients with schizophrenia, bipolar I disorder and unaffected first-degree relatives
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Abstract

Disruption of the balance between excitation and inhibition (E/I balance) is a leading hypothesis for pathophysiology of neuropsychiatric disorders, e.g. schizophrenia. However, it is poorly understood how synaptic-level E/I disruptions propagate upward to induce behavioral-level cognitive deficits. To link these levels, we have developed a framework for Computational Psychiatry using biophysically-based models of neural circuits to study how neural activity and cognitive behaviors are impacted by disease-related synaptic perturbations.

Here, we studied models of cortical circuits that perform cognitive computations such as working memory and decision making. Motivated by hypotheses for neuropathology associated with schizophrenia, we tested effects of hypofunction of NMDA receptors at two key sites: on inhibitory interneurons (elevating E/I ratio via disinhibition), versus on excitatory pyramidal neurons (reducing E/I ratio).

For working memory, we found disinhibition broadens the tuning of mnemonic, stimulus-selective persistent activity patterns; we tested this prediction using behavioral data from human subjects performing a spatial working memory task combined with ketamine infusion. The model further predicts increased behavioral variability degrading mnemonic precision, and impaired filtering of distractors. To test these predictions, we designed and tested behavioral tasks for patients with schizophrenia.

For decision making, we found disruption of E/I balance in either direction can impair performance as assessed by psychometric functions. Nonetheless, these two regimes make dissociable predictions for the time course of evidence accumulation. Under elevated E/I ratio, behavior is “impulsive”: evidence early in time is weighted more than evidence late in time, compared to control. Under reduced E/I ratio, behavior is “indecisive”: the circuit exhibits weakened integration and reduced winner-take-all competition.

Our findings highlight the importance of cortical E/I balance in cognitive functions. These models make specific predictions for behavior and neural activity that are testable in humans or animals under manipulation of E/I balance (e.g. via pharmacology) or in disease states.