Cognitive Enhancement Effects of *Bacopa monnieri* (Brahmi) on Novel Object Recognition and Neuronal Density in the Prefrontal Cortex, Striatum and Hippocampus in Sub-Chronic Phencyclidine Administration Rat Model of Schizophrenia

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Background: *Cognitive deficit is a significant problem, which finally occurs in all schizophrenic patients. It can not be attenuated by any antipsychotic drugs. It is well known that changes of neuronal density are correlated with learning and memory deficits. Bacopa monnieri (Brahmi), popularly known as a cognitive enhancer, might be a novel therapeutic agent for cognitive deficit in schizophrenia by changing cerebral neuronal density. The objective of this study was to determine the effects of Brahmi on attenuation at cognitive deficit and on the neuronal density in the prefrontal cortex, striatum and cornu ammonis subfield 1 (CA1) and 2/3 (CA2/3) of hippocampus in sub-chronic phencyclidine (PCP) rat model of schizophrenia.*
Material and Method: *Rats were assigned to three groups; Group-1: Control, Group-2: PCP administration and Group-3: PCP + Brahmi. Rats were tested for cognitive ability by using the novel object recognition test. Neuronal density from a serial Nissl stain sections of the prefrontal cortex, striatum and hippocampus of rat model of schizophrenia were measured by using Image ProPlus software and manual counting.*
Results: *Sub-chronic administration of PCP results in cognitive deficits in novel object recognition task. This occurred alongside significantly increased neuronal density in CA1. The cognitive deficit was recovery to normal in PCP + Brahmi group and it occurred alongside significantly decreased neuronal density in CA1. On the other hand, significantly increased neuronal density was observed in CA2/3 of PCP + Brahmi group compared with PCP alone.*
Conclusion: *Brahmi is a potential cognitive enhancer against schizophrenia. It reduces neuronal density, most likely glutamatergic neuron, which results in neuronal toxicity and cognitive deficit. Therefore, Brahmi has cognitive enhancement effect by reducing glutamatergic neuron in CA1. Moreover, it also has neurogenesis effect in CA2/3, which is needed to be investigated in the further study.*

Keywords: *Brahmi, Schizophrenia, Animal model, Neuronal density, Novel object recognition*

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Of the many psychological diseases being researched, schizophrenia is included in the priority group of diseases that directly affects the life of the patient as well as family and relatives of the patient. It is found in about 1% of the world's population including Thailand and there is evidence that this percentage will continue to increase. Medical and scientific researchers have tried to discover the cause of this psychological disease. Some of the common accepted ideas include genetics, abnormalities of the brain at birth[1] and abnormal neurotransmitters in the brain such as dopamine, γ-Aminobutyric acid (GABA), serotonin and glutamate both in the quantity and in the energy sent to the receptors or transporters of the brain[2-5].

According to the American Association of Psychiatry (DSM-IV, 1994) and the World Health Organization International Classification of Diseases (ICD-10, 1992), the most common symptoms of this disease are positive (e.g. hallucinations, delusions, disorganized speech, disorganized behavior) and negative (e.g. social withdrawal) symptoms[6]. Recently

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it has been discovered that one very important symptom that greatly affects the everyday life of the patient is cognitive impairment in learning and memory[7].

Several schizophrenia models have been developing in biological psychiatry research. The administration of psychotomimetic drugs to human and animals is widely accepted and utilized as a model for schizophrenia. Phencyclidine (PCP) is a common drug known for blocking NMDA-mediated transmission by binding to a site within the ion pore of the NMDA receptor. The effects of non-competitive NMDA antagonist in human and animals have been widely studied to clarify the understanding of pathophysiology of schizophrenia.

Rats receiving sub-chronic PCP administration have shown behavioral changes such as hyperlocomotion, enhanced stereotypic behaviors, cognitive and sensorimotor gating deficits and impaired social interactions which correspond to symptoms found in schizophrenia[8]. It has also been confirmed that sub-chronic PCP administration can also produce impairment of learning and memory in rats[9] and cortical apoptosis and neuronal loss[10], possibly implicating cognitive deficit in schizophrenia.

Memory impairment is often recognized as the earliest symptom of Alzheimer's disease (AD). Therefore, a lot of research has focused on neuropathological changes and neuronal density in the enthorinal cortex (EC) of AD patients suggesting their contribution to memory impairment at mild stages of Alzheimer's disease. Some studies have been able to prove that neuronal loss does not occur in the EC of cognitively intact elderly, whereas there is a selective and very dramatic loss of neurons in the same region even in the mildest stages of dementia in AD. This suggests a correlation between damage of EC and neuropathological changes with memory impairment[11,12]. An investigation of area 9 of the cerebral cortex in schizophrenic patients resulted in increased neuronal and glial densities though the elevation in glial density was not significant[13]. Neuronal loss in the Prefrontal cortex, Striatum and Hippocampus related to memory impairment[14] might be contributed to the cognitive deficit in schizophrenia. However, little attention has been paid to the neuronal density in the brain of schizophrenic patients.

Typical antipsychotic drugs have been shown a great impression on reducing positive symptoms and disabilities in schizophrenia; however, they can produce extrapyramidal movement disorders[15]. Moreover, they are not effective at attenuating negative symptoms[16]. To date, atypical antipsychotic drugs have been defined as highly effective drug treatment in schizophrenia due to the capability of reducing the incidence of extra-pyramidal symptoms and alleviating the negative symptoms, however, they are more likely to induce weight gain and obesity related diseases[17].

As mentioned earlier, cognitive impairment is a major problem, which leads to functional disability in schizophrenia. It finally occurs in all schizophrenic patients. Neither typical nor atypical antipsychotics can enhance cognitive function in the patients. There is evidence to suggest that some alternative medicines may have cognitive enhancement effects. *Bacopa monnieri* or Brahmi is a traditional Indian Ayurvedic medicinal plant, which has been defined as an herbal therapeutic that boosts memory, restores cognitive deficits and improves mental function[18]. Recent study has reported that long-term orally administration of bacosides, the active saponins of Brahmi, can prevent age-associated neuro-degeneration and promote healthy brain ageing in female Wistar rats[19]. Additionally, it has been reported that Brahmi can reduce beta-amyloid levels in the brain of transgenic mouse model of Alzheimer's disease[20]. Consistent with the study in human, Brahmi extract has been reported to enhance cognitive performance in ageing[21]. Therefore, Brahmi might be able to recover the cognitive function in the schizophrenic patients.

The main aim of the present study was to assess whether administration of Brahmi was able to recover the cognitive deficit which could be developed in sub-chronic PCP administration rat, assessed using the novel object recognition paradigm, and on the neuronal density in the prefrontal cortex, striatum and hippocampus.

Material and Method

Animals

Thirty-six male Wistar rats weighing 200 to 220 g were obtained from the National Animal Center, Mahidol University, Thailand. The animals were housed one per cage and maintained at 21±2°C under a 12-hour light/dark cycle with food and water available ad libitum in the home cage. All animals were acclimatized for seven days before experiment. All animal procedures were carried out in accordance with Mahidol University Code of Practice and the National Institutes of Health (USA) Guidelines for treatment of laboratory animals. The protocol for the present study was approved by the Animal Research Committee of Thammasat University,

Thailand. The number of project license for animal experiment in the present study is AE 008/2552.

Drugs and drug administration

Animals were assigned to three groups (n = 12/group);

Control group

Animals received vehicle solution (0.9% NaCl) ip bi-daily (08:00 and 16:00) for seven days. They then orally received vehicle solution (distilled water) daily (08:00 h) for further 14 days.

Sub-chronic PCP group

Animal received 2 mg/kg of PCP ip bi-daily (08:00 and 16:00) for seven days. They then orally received vehicle solution (distilled water) daily (08:00 h) for further 14 days.

PCP + Brahmi group

Animals received 2 mg/kg of PCP ip bi-daily (08:00 and 16:00) for seven days. They then orally received 40 mg/kg/day of Brahmi daily (08:00 h) for further 14 days. PCP HCl (Sigma, USA) and Brahmi (Planetary™ Herbals) were dissolved in 0.9% NaCl and distilled water, respectively.

Novel object recognition test

A novel object recognition test was performed on all groups of animals a week after drugs or vehicle administration. The test took place in a room with 360 lux lighting. The apparatus consisted of a solid black plastic box (63 cm x 63 cm x 45 cm), which was placed on the floor throughout the experiment. A video recorder (Canon) was positioned on a movable trolley above the plastic box in order to record behavior. The objects to be discriminated were made of glass, plastic or ceramic. During the task, the bottoms of objects were fixed by adhesive tape in order not to be displaced by the animals. In the three days prior to the novel object, recognition test, all rats were initially habituated to the empty box for three sessions of three minutes daily. In the novel object recognition test, each rat was placed in the box and exposed for three minutes to two identical objects placed approximately 10 cm apart in the center of the box. The rat was then returned to its home cage for an hour. The box and the objects were cleaned with 70% ethanol. Both objects in the box were replaced, one with an identical object and another with a novel object. Rats were then returned to the novel object recognition box and allowed to explore the objects for three minutes. All trials were recorded and behavioral analysis was carried out blind to treatment. Object exploring included rat sniffing, licking, or touching the objects. The data were expressed as the discrimination ratio (DR) calculated from the following equation; DR = [(time exploring novel object-time exploring familiar object)/total exploration time)]. The data are expressed as mean $\pm$ SEM. One-way ANOVA was performed to determine the effect of treatment on DR value, followed by post hoc statistical comparison of treatment group. An independent t-test was used to compare DR value between PCP and PCP with Brahmi groups. Statistical significances were defined as $p<0.05$. All statistical analysis were performed using SPSS V13 for windows (SPSS Inc., Chicago, USA). After the novel object recognition test was completed, all rats were sacrificed and whole brains were removed and preceded to Nissl-staining and neuronal density measurement.

Neuronal density measurement

Tissue preparation and Nissl-staining

After all brains were removed, they were fixed in 4% paraformaldehyde. All animal brain tissues were paraffin-embedded sections, which were sectioned coronally at a thickness of 5 μm then mounted onto the slide. For the sectioning, levels with respect to Bregma were determined with the use of a rat brain stereotaxic atlas. The sections for prefrontal cortex were taken between Bregma 2.7 to 2.2 mm while those for striatum were taken from Bregma 0.7 mm. Sections for hippocampus were sectioned posterior to Bregma 3.3 mm. All sections were dewaxed in xylene then rinsed in 100%, 95%, 90%, 80%, and 10% ethanol and washed for 5 minutes in distilled water. The sections were then stained with in cresyl violet 20 minutes, and washed in distilled water then placed in 70%, 80% and 90% ethanol. The sections were left in 95% ethanol until excess stain has been removed, then passed through absolute alcohol into three changes of xylene and mounted with permount, covered with a cover slip and then viewed under light microscope. The pictures were captured by using Image ProPlus software and neuronal density was manually counted in prefrontal cortex, striatum and CA1 and CA2/3 of hippocampus. Twenty-four 2x2 cm^2 templates were made and used for the neuronal density counting in each area of interest.

Results

Novel object recognition test

One-way ANOVA with Dunnett post hoc tests revealed a significant reduction in discrimination ratio

in sub-chronic administration of PCP compared with control (p<0.001). Independent t-test revealed a significant increase in DR score in PCP with Brahmi (p<0.001) compared with PCP alone. DR score is significantly increased in PCP + Brahmi compared with control (p<0.01) (Fig. 1).

Neuronal density measurement

Nissl staining demonstrated cell body, neural processes scattered in prefrontal cortex, striatum, CA1 and CA2/3 (Fig. 2). Neuronal density was measured in the prefrontal cortex. One-way ANOVA with Dunnett post hoc tests revealed a decreased neuronal density in PCP group compared with control although it was not significantly different. A decrease in neuronal density was observed in PCP treated with Brahmi group compared with control (post hoc Dunnet) and PCP group (independent t-test). However, there were no significant differences (Fig. 3). Fig. 4 showed no significant difference of neuronal density in striatum of PCP and PCP + Brahmi group compared with control (post hoc Dunnet) and also between PCP + Brahmi and PCP (independent t-test). However, neuronal density tended to increase in PCP group compared with control and decreased after Brahmi administration. Fig. 5 revealed the significant increase in neuronal density in CA1 of PCP group compared with control (p<0.01). There were a decreased neuronal density in PCP + Brahmi group compared with control (p<0.001). Comparing between PCP + Brahmi group and PCP showed a significant decreased in neuronal density in PCP + Brahmi group (p<0.01). Fig. 6 revealed that neuronal density in PCP was increased compared with control although it was not significantly different. There was an increased neuronal density in PCP + Brahmi group compared with control although it was not significantly different. There was a significant increase in neuronal density in CA2/3 of PCP + Brahmi compared with PCP group (p<0.05).

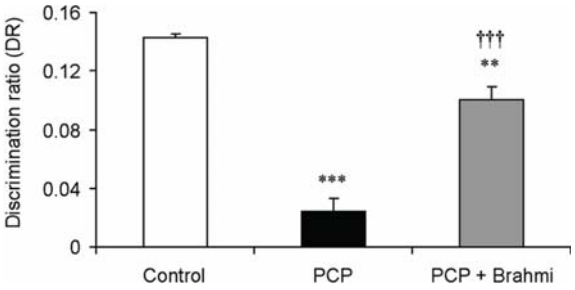

Fig. 1 Discrimination ratio in control, PCP and PCP with Brahmi groups obtained from novel object recognition test. Data are mean ± SEM. **p<0.01, ***p<0.001 vs. control, ^{+++}p<0.001 vs. PCP.

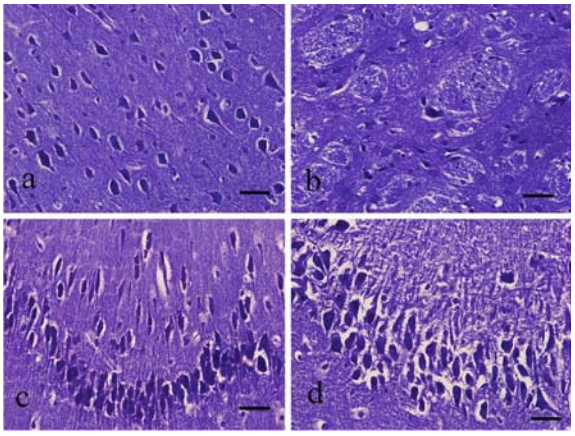

Fig. 2 Nissl-staining of coronal sections showing neuronal density in the prefrontal cortex (a), striatum (b), and CA1, CA2/3 (c, d) of sub-chronic phencyclidine rat model of schizophrenia (40x magni-fication). Bar 50 µm.

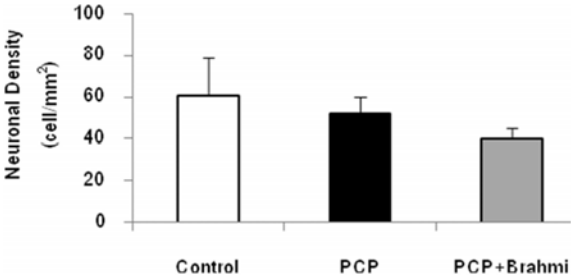

Fig. 3 Neuronal density fromNissl staining technique in prefrontal cortex of control, PCP and PCP with Brahmi groups. Data are mean ± SEM.

Discussion

The present study showed deficits in novel object recognition in animals receiving sub-chronic PCP administration. The deficits in DR scores in this animal group occurred alongside increase in neuronal density in striatum, CA1 and CA2/3 however, it is significant only in CA1. It is possible that this increase of neuronal density is due to the increase of glutamatergic neurons[22]. It has been reported that up-regulation of glutamatergic neurons produce neurotoxicity and neuronal cell death[23], which leads to cognitive deficit behavioral disorders[24]; therefore, increase in neuronal density, possibly the glutamatergic neuron may induce the neuronal cell death, which might be implicated in cognitive deficit found in schizophrenia. Moreover, it

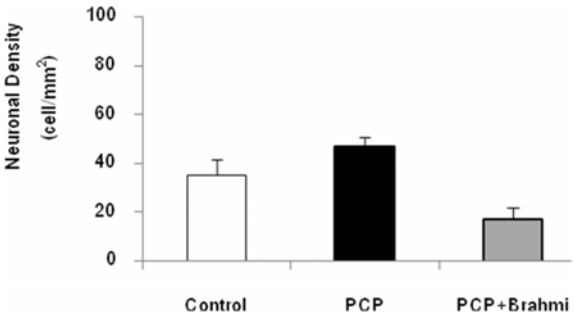

Fig. 4 Neuronal density from Nissl staining technique in striatum of control, PCP and PCP with Brahmi groups. Data are mean ± SEM.

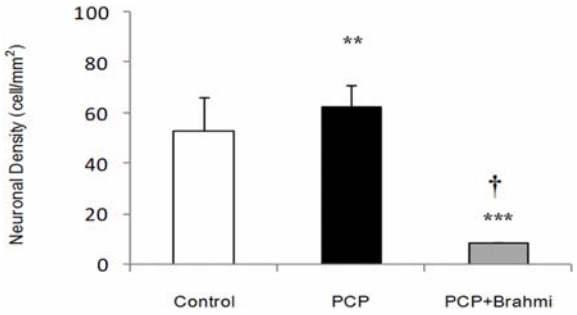

Fig. 5 Neuronal density from Nissl staining technique in CA1 of control, PCP and PCP with Brahmi groups. Data are mean ± SEM. ** $p<0.01$, *** $p<0.001$ vs. control, $^{+}$ $p<0.05$ vs. PCP.

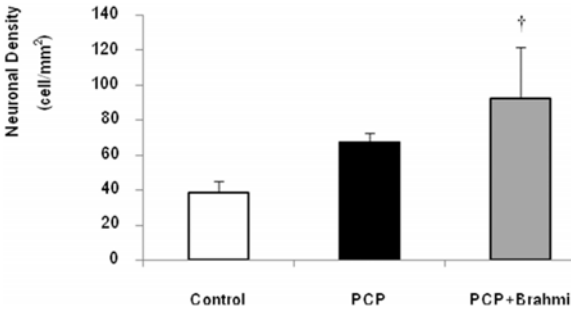

Fig. 6 Neuronal density from Nissl staining technique in CA2/3 of control, PCP and PCP with Brahmi groups. Data are mean ± SEM. $^{+}$ $p<0.05$ vs. PCP.

has been reported that CA1 and CA2/3 play an important role in memory and cognition[15]. Increase of glutamatergic neuron resulting in neuronal cell death leads to memory and cognition impairment found in this PCP administration rat model.

An increased neuronal density could be the result of a decreased hippocampal area of subfields CA1 and CA2/3 (volumetric reduction of hippocampal subfields). However, no volumetric reduction of the hippocampus or its component substructures in animals receiving sub-chronic PCP administration was evident in the present study. Therefore, it is unlikely that an increased neuronal density in the present study resulted from a volumetric reduction but rather a correlation of neuronal pathology. Results are consistent with other MRI studies reporting no significant changes of thalamic volume in schizophrenic patients[25] as well as no reduction of hippocampal volume in subjects with a high risk of psychosis[26].

However, some MRI studies have reported a volumetric reduction of hippocampus in schizophrenia including: 1) bilateral volumetric reduction of hippocampus in schizophrenia[27]; 2) reduction of the left parahippocampal gyrus in male and female schizophrenia; 3) reduction of both sides of hippocampus in female schizophrenia; and 4) smaller total brain size in chronic schizophrenic patients. Volumetric reduction of other brain regions has also been observed in schizophrenia such as an increase of amygdala volume in male schizophrenia, the reduction of insular cortex volume in schizophrenic patients and bilateral volume reductions in the anterior limb of the internal capsule in patients with schizophrenia[28]. Inconsistencies remain regarding the volumetric reduction of the brain in schizophrenia. This present study showed no evidence of a volumetric reduction of hippocampus in schizophrenia.

Prefrontal cortex is responsible for cognitive function[29-31], therefore the decreased of neuronal density in prefrontal cortex in sub-chronic PCP administration group found in the present study although it is not significant difference might be the decreased of all neurons found in this area which contributes to the cognitive deficit.

Nissl-staining in sub-chronic PCP administration receiving Brahmi revealed a decrease in neuronal density in the prefrontal cortex, striatum and CA1 although it is significant difference only in CA1. These results suggested that Brahmi administration after sub-chronic PCP appeared to have an effect on reduced glutamatergic neuron in these brain regions especially in CA1 that mainly contribute to cognitive function and memory[32]. Therefore, the present study suggested that Brahmi was able to recover cognitive function by reducing glutamatergic neuron in CA1. These findings are consistent with other publications. The long-term oral administration of bacosides (active sapponins of Brahmi) can prevent age-associated neuro-degeneration and promote healthy brain aging

in female Wistar rats as well as reduce beta-amyloid levels in the brain of transgenic mice models of Alzheimer's disease. The Brahmi extract is able to enhance cognitive performance in aging, which is also consistent with studies made on human models.

The present study was able to show a significant increase of neuronal density in CA2/3 in PCP + Brahmi. This strongly suggests that the use of Brahmi could result in a neurogenesis effect in CA2/3 increasing the cognitive function assessed by novel object recognition tasks. Similar studies have drawn the same conclusions that Brahmi could increase learning and memory tasks as well as have an effect on neurogenesis[22]. However, the effect on neurogenesis is a subject requiring further investigation.

Conclusion

Sub-chronic administration of PCP results in cognitive deficits in novel object recognition tasks. It occurred alongside with the significant increase of neuronal density in CA1, which might be the up-regulation of glutamatergic neuron resulting in neuronal toxicity. This cognitive deficit can be recovery to normal after receiving Brahmi and this occurred alongside with the decrease of neuronal density in CA1. Therefore, we concluded that Brahmi has a cognitive enhancement effect. The administration of Brahmi has been shown to not only provide cognitive enhancement but also a neurogenesis effect. This study suggests that the use of Brahmi is a valuable alternative medicine able to combat cognitive impairment in the PCP administered rat models of schizophrenia with the potential of increasing the wellness of life of psychotic patients.

Acknowledgement

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Potential conflicts of interest

None.

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ฤทธิ์กระตุ้นการเรียนรู้และความจำของ Bacopa monnieri (พรมมิ) ต่อการแยกแยะวัตถุใหม่และต่อปริมาณของเซลล์ประสาทในสมองส่วน prefrontal cortex, striatum และ hippocampus ในหนูที่ถูกเหนี่ยวนำให้เป็นโรคจิตเภทด้วย sub-chronic phencyclidine

ธนิศรา เวชเตง, ปริศนา ปียะพันธุ์

ภูมิหลัง: *การเรียนรู้และความจำบกพร่องเป็นอาการสำคัญที่ในท้ายที่สุดจะเกิดขึ้นกับผู้ป่วยโรคจิตเภททุกราย ซึ่งไม่สามารถรักษาได้ด้วยยาในกลุ่ม antipsychotics เป็นที่ทราบกันดีว่าการเปลี่ยนแปลงของเซลล์ประสาท มีความสัมพันธ์กับการสูญเสียความสามารถในการเรียนรู้และความจำพรมมิ ซึ่งเป็นที่รู้จักกันอย่างแพร่หลาย ในการช่วยกระตุ้นการเรียนรู้และความจำอาจเป็นแนวทางใหม่ของการรักษาการเรียนรู้และความจำที่ลดลงในโรคจิตเภท โดยมีผลต่อปริมาณเซลล์ประสาทในสมอง*

วัตถุประสงค์: *เพื่อศึกษาผลของพรมมิต่อการเรียนรู้และความจำที่ลดลงและต่อปริมาณของเซลล์ประสาทในสมองส่วน prefrontal cortex, striatum และ cornu ammonis fields 1 (CA1) and 2/3 (CA2/3) ของหนูที่ถูกเหนี่ยวนำให้เป็นโรคจิตเภทด้วย sub-chronic phencyclidine (PCP)*

วัสดุและวิธีการ: *หนูถูกแบ่งเป็น 3 กลุ่ม คือ กลุ่ม 1 กลุ่มควบคุม, กลุ่ม 2 ได้รับ PCP และกลุ่ม 3 ได้รับ PCP จากนั้นได้รับพรมมิ (PCP + Brahmi) หนูทุกกลุ่มถูกทดสอบความสามารถในการเรียนรู้และความจำ ซึ่งได้มาจากการทดสอบการแยกแยะวัตถุใหม่ (novel object recognition) ปริมาณของเซลล์ประสาทในสมองส่วน prefrontal cortex, striatum และ hippocampus ถูกวัดด้วยโปรแกรม Immage ProPlus และ manual counting*

ผลการศึกษา: *การได้รับ PCP ทำให้ความสามารถในการเรียนรู้และความจำซึ่งได้มาจากการทดสอบการแยกแยะ วัตถุใหม่ลดลงซึ่งเกิดขึ้นร่วมกับการเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติของปริมาณเซลล์ประสาทสมองส่วน CA1 การลดลงของความสามารถในการเรียนรู้และความจำนี้กลับเป็นปกติในหนู PCP ที่ได้รับ Brahmi และเกิดขึ้นร่วมกับการลดลงอย่างมีนัยสำคัญทางสถิติของปริมาณเซลล์ประสาทสมองส่วน CA1 ในทางตรงกันข้าม พบว่ามีการเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติของปริมาณเซลล์ประสาทสมองส่วน CA2/3 ในหนูกลุ่ม PCP + Brahmi เปรียบเทียบกับหนูที่ได้รับ PCP อย่างเดียว*

สรุป: *พรมมิสามารถฟื้นฟูการเรียนรู้และความจำในโรคจิตเภทได้โดยลดปริมาณเซลล์ประสาทซึ่งน่าจะเป็น glutamatergic neuron ซึ่งปกติแล้วมีผลทำลายเซลล์ประสาทและทำให้สูญเสียความสามารถในการเรียนรู้และความจำ ดังนั้นพรมมิจึงมีผลกระตุ้นการเรียนรู้และความจำได้โดยลด glutamatergic neuron ใน CA1 นอกจากนั้นยังมีผลทำให้เกิด neurogenesis ใน CA2/3 ซึ่งจะต้องทำการทดลองเพิ่มขึ้นในอนาคต*