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Zinc Signaling in the Hippocampus and Its Relation to Pathogenesis of Depression

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Abstract Zinc is released from glutamatergic (zincergic) neuron terminals in the brain, followed by the increase in Zn^{2+} concentration in the intracellular (cytosol) compartment as well as that in the extracellular compartment. Intracellular Zn^{2+} concentration mainly increases through calcium-permeable channels and serves as Zn^{2+} signal as well as extracellular Zn^{2+} concentration. Hippocampal Zn^{2+} signaling may participate in synaptic plasticity such as long-term potentiation and cognitive function. On the other hand, subclinical zinc deficiency is common in the old who might be more susceptible to depression. Zinc deficiency causes abnormal glucocorticoid secretion and increases depression-like behavior in animals. Neuropsychological symptoms are observed prior to the decrease in Zn^{2+} signal in the hippocampus under zinc deficiency. This paper summarizes that hippocampal Zn^{2+} signaling serves to maintain healthy brain and that glucocorticoid signaling, which is responsive to zinc homeostasis in the living body, is linked to the pathophysiology of depression.

Keywords Zinc · Signaling · Homeostasis · Depression · Hippocampus · Aging

Introduction

The importance of zinc has been reported in human health [1, 2]. Approximately, 50% of the world population is at the risk of zinc deficiency [3] and 10% of the North American population consumes less than half the recommended daily allowance for zinc [4].

Zinc is essential for cell division and differentiation [5]. Over 300 proteins require zinc for their functions in microorganisms, plants, and animals. The importance of zinc is true of the brain [6, 7]. Zinc concentration in the brain increases with the development and reaches approximately 200 μM in the adult [8]. Extracellular zinc concentration in the adult brain is estimated to be less than 1 μM [9], and zinc concentration in the cerebrospinal fluid (CSF) is approximately 0.15 μM [10] which is much lower than in the plasma (approximately 15 μM). The blood–CSF barrier participates in zinc transport from the plasma to the CSF [11] and, in addition to the blood–brain barrier, is involved in zinc homeostasis in the brain [12, 13] (Fig. 1). Zinc is relatively concentrated in the hippocampus and amygdala (the biological half-life, hippocampus, 28 days; amygdala, 42 days) [14]. However, zinc homeostasis in the brain is spatiotemporally altered in neurological diseases and involved in pathophysiology [15–18].

Approximately 80% of the total brain zinc exists as zinc metalloproteins. The rest mainly exists in the presynaptic vesicles and is histochemically reactive as revealed by Timm's sulfide-silver staining method [19–21]. The removal of zinc transporter-3 (ZnT-3) protein, which is responsible for the movement of zinc from the cytoplasm into synaptic vesicles, results in a 20% reduction of the total amount of zinc in the brain [22]. Histochemically reactive zinc is released along with neuronal activity; there is a large number of evidence on zincergic neurons that sequester zinc in the presynaptic vesicles and release it in a calcium- and impulse-dependent manner. In the rat brain, Timm's stain is hardly observed just after the birth and its intensity increases with

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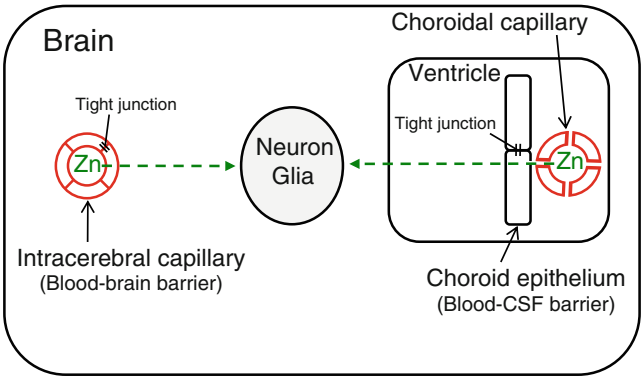

Fig. 1 Brain barrier system and zinc transport into the brain parenchyma cells through the brain barrier system. The blood–brain and the blood–CSF barriers consist of the tight junction between the brain capillary endothelial cells and the tight junction between the choroidal epithelial cells, respectively

brain development [23, 24], indicating that histochemically reactive zinc is involved in not only brain growth but also brain function.

The exact chemical form of histochemically reactive zinc is unknown. The zinc released in the extracellular space is estimated to serve in free form (Zn^{2+}) [1]. The basal Zn^{2+} concentrations are extremely low in both the extracellular (~10^{-8} M) [25] and intracellular (<10^{-9} M) compartments [26]. Zn^{2+} concentration increases in both compartments by excitation of zincergic neurons and serves as a signal [27]. Furthermore, other organelles including the cytoplasm may participate in the increase in cytosolic Zn^{2+} [28–30]. The mechanisms on Zn^{2+} homeostasis and its dynamics are poorly understood.

The hippocampus plays an important role in learning, memory, and recognition of novelty [31]. The hippocampus receives major input from the entorhinal cortex via the perforant pathway, the dentate granule cells project to the CA3 pyramidal cells via the mossy fibers, and the CA3 pyramidal cells project to the CA1 pyramidal cells via the Schaffer collaterals. The three pathways are glutamatergic (zincergic) [32]. It has been reported that histochemically reactive zinc serves as an endogenous neuromodulator of several important receptors including the α-amino-3-hydroxy-5-*methyl*-4-isoxazolepropionic acid (AMPA)/kainate receptor, *N-methyl*-D-aspartate (NMDA) receptors and γ-amino butyric acid (GABA) receptors [33]. The zinc seems to participate in synaptic plasticity such as long-term potentiation (LTP) and long-term depression that is believed as the mechanism of learning and memory [34, 35]. The hippocampus also participates in stress response, which may change synaptic Zn^{2+} dynamics [36], and is vulnerable to stress.

This paper summarizes that Zn^{2+} signaling is closely linked to hippocampus function. On the basis of the evidence that serum zinc decreases in the old [37] who appears to be at more risk for depression [38], furthermore, the importance of zinc homeostasis in the pathophysiology of depression is summarized in association with the hypothalamo-pituitary-adrenocortical (HPA) system activity. On the other hand, neurological alterations in the frontal cortex are also important in the pathophysiology of depression. Although the changes in gene expression such as zinc transporter in rat depression model and methallothionein, a zinc-binding protein in major depression are reported in the frontal cortex to understand the etiology of depression, the evidence on Zn^{2+} signaling is limited [39–41]. Thus, this paper focuses on hippocampal Zn^{2+} signaling and its relation to the pathogenesis of depression.

Zn^{2+} Signaling and Hippocampal Function

Presynaptic Zinc Action

The significance of the increase in extracellular Zn^{2+} is examined in the rat hippocampus by using in vivo microdialysis. In the hippocampal CA3 and CA1 regions, glutamate concentration in the extracellular fluid is decreased in the presence of 10–300 μM $ZnCl_2$, while increased in the presence of 1-mM calcium ethylenediaminetetraacetic acid (CaEDTA), a membrane-impermeable zinc chelator [42, 43]. In contrast, GABA concentration in the extracellular fluid is increased in the presence of zinc. Because zinc blocks GABA transporter 4, this blockade may increase extracellular GABA concentration [44]. In interneurons, GABA release might be facilitated through the zinc-mediated potentiation of AMPA/kainate receptors [43]. The increase in extracellular Zn^{2+} may differentially act on glutamatergic and GABAergic neurotransmitter systems in the hippocampus. Zinc-mediated GABA release attenuates glutamate release, especially in glutamate-induced excitotoxicity [44].

Zn^{2+} released from zincergic neuron terminals is immediately retaken up by the same terminals during tetanic stimulation and also taken up into postsynaptic neurons [27, 45] (Fig. 2). Calcium channels such as calcium-permeable AMPA/kainate receptors are involved in Zn^{2+} influx during synaptic excitation [9, 26, 46, 47]. Kainate receptors that are abundantly expressed in mossy fibers might be involved in Zn^{2+} influx into mossy fiber terminals [48].

Quinta-Ferreira and Matias [49, 50] report that Ca^{2+} influx into mossy fibers by tetanic stimulation is inhibited by endogenous zinc. Zn^{2+}-mediated inhibition of Ca^{2+} influx into the presynaptic terminals after tetanic stimulation, which may lead to negative modulation of the presynaptic activity, is also observed in the CA1 [45]. In an experiment using synaptosomal fraction from rat hippocampal CA3, Zn^{2+} inhibits glutamate release via

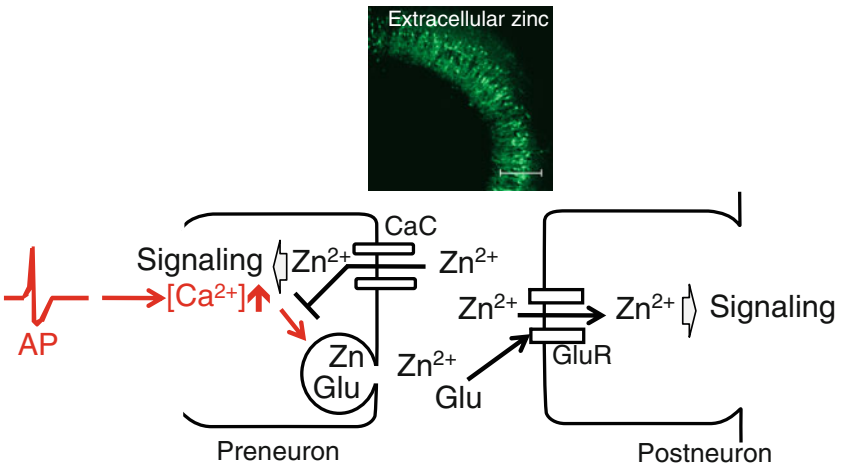

Fig. 2 Zn^{2+} signaling in the hippocampus. Zn^{2+} released from zincergic neuron terminals is immediately taken up into presynaptic and postsynaptic neurons through calcium-permeable channels (CaC and GluR). Zn^{2+} signaling participates in not only synaptic neurotransmission but also synaptic plasticity such as LTP. In pathological condition, the negative modulation of presynaptic activity by Zn^{2+} signaling may protectively serve against postsynaptic neurodegeneration that is linked with glutamate excitotoxicity. An inserted panel represents extracellular zinc in the synaptic clefts in the stratum lucidum, which is imaged with ZnAF-2, a membrane-impermeable zinc indicator

activation of presynaptic ATP-dependent potassium (K_{ATP}) channels [51]. Zn^{2+} released from zincergic neuron terminals may serve for negative feedback mechanisms against glutamate release in both the extracellular and intracellular compartments [27, 45] (Fig. 2).

Postsynaptic Zinc Action

Mossy fiber activity elicits Ca^{2+} influx via NMDA receptors and voltage-dependent calcium channels (VDCC) and intracellular Ca^{2+} mobilization via group I metabotropic glutamate receptors in CA3 pyramidal cells [52]. Zinc is a blocker of NMDA receptors and VDCC [33]. However, the increase in extracellular Zn^{2+} concentration might be insufficient for their blockades as described later. On the other hand, the increase in postsynaptic Zn^{2+} concentration decreases the basal Ca^{2+} concentration in CA3 pyramidal cells under the resting condition [47]. On the basis of this evidence, the role of Zn^{2+} signaling in Ca^{2+} signaling in postsynaptic neurons is examined in hippocampal slices. The increase in intracellular Zn^{2+} suppresses Ca^{2+} mobilization induced by a group I metabotropic glutamate receptor agonist, *trans*-azetidine-2,4-dicarboxylic acid, suggesting that Zn^{2+} signaling can negatively modulate intracellular Ca^{2+} mobilization via group I metabotropic glutamate receptor pathway in CA3 pyramidal cells [47].

Zn^{2+} Signaling in Hippocampal LTP

Synaptic plasticity has been extensively researched in the hippocampus [53]. It is thought that neural circuits of zincergic neurons are associated with the episodic memory function and are important for behavior, emotional expression and cognitive-mnemonic operations [12, 35, 54]. However, the role of Zn^{2+} signaling in the acquisition, storage and retrieval of memory remains to be solved.

Extracellular Zn^{2+} increases frequency-dependently after delivery of electrical stimulation to mossy fibers [55]. Extracellular zinc concentration after tetanic stimulation is estimated to range between 10 and 100 μM, because the low-affinity site (IC_{50}≈20 μM at −40 mV) of NMDA receptors is bound by zinc [56]. On the basis of the hypothesis that exogenous zinc potentiates the action of zinc released from mossy fiber terminals, mossy fiber LTP is induced in the presence of $ZnCl_2$ at low micromolar concentrations. Mossy fiber LTP is significantly attenuated in the presence of 5 μM $ZnCl_2$ [57], suggesting that endogenous Zn^{2+} negatively modulate mossy fiber LTP. Zn^{2+} concentration is likely to reach very low micromolar concentrations in the extracellular compartment during the LTP induction. Judging from the evidence that the IC_{50} of Zn^{2+} against recombinant adenyl cyclase I is 1.4 μM [58], Zn^{2+} may suppress the cAMP-protein kinase A signaling pathway via inhibition of adenyl cyclase I in mossy fiber boutons, followed by Zn^{2+}-mediated modulation of mossy fiber LTP [48].

CA1 LTP at the Schaffer collateral/commissural synapses is completely inhibited in the presence of 100 μM zinc [59], suggesting that this inhibition is due to the block of NMDA receptors by Zn^{2+}. The evidence that CaEDTA inhibits CA1 LTP [59, 60] suggests that endogenous Zn^{2+} participates in the induction of CA1 LTP. Furthermore, CA1 LTP induced by tetanic stimulation (100 Hz, 1 s),

which is completely blocked in the presence of 2-amino-5-phosphonovalerate (APV), a NMDA receptor antagonist, is potentiated in the presence of 1–5 μM $ZnCl_2$, suggesting zinc-mediated potentiation of NMDA receptor-dependent CA1 LTP [60]. In contrast, CA1 LTP induced by a 200-Hz tetanus for 1 s in the presence of APV is not potentiated in the presence of 5 μM $ZnCl_2$, indicating that NMDA receptor-independent CA1 LTP is not potentiated with Zn^{2+} [61].

Numerous pharmacological and molecular genetic manipulations have led to alteration in both hippocampal LTP and memory formation. It is believed that LTP is a cellular model of learning and that an LTP-like mechanism is involved in the initial encoding of the information, at least in the hippocampus, where this information is maintained for a significant period of time before being potentially transferred to the cortex [62–64]. In the recall, those circuits that have been potentiated during learning may be reactivated preferentially over nonpotentiated pathways [65]. Clioquinol, a membrane-permeable zinc chelator transiently reduces Zn^{2+} signaling in the hippocampus, especially in the dentate gyrus, and attenuates dentate gyrus LTP, followed by the impairment of recognition memory [66]. Thus, hippocampal Zn^{2+} signaling is likely to be involved in memory formation (Fig. 2).

Zn^{2+} Signaling in Glutamate Excitotoxicity

In both the extracellular and the intracellular compartments, it is possible that zinc signaling plays a neuroprotective role against glutamate-induced excitotoxicity. Activation of presynaptic kainate receptors is involved in the release of zinc and glutamate from mossy fibers [67, 68]. Astrocytes also release glutamate [69]. Loss of astrocyte glutamate homeostasis is a prerequisite for the excitotoxic cascade, a phenomenon that is becoming recognized in an increasing number of neurological disorders [70, 71]. Zn^{2+} may negatively modulate Ca^{2+} mobilization in CA3 pyramidal cells after regional delivery of glutamate (1 mM) to the stratum lucidum, where mossy fibers exist, suggesting that Zn^{2+} attenuates glutamate excitotoxicity through the action as a negative feedback factor (Fig. 2) [72]. On the other hand, excessive Zn^{2+} influx into postsynaptic neurons is neurotoxic [73–78]. Côté et al. [79] report that the neurotoxic and neuroprotective actions of Zn^{2+} depend on its concentration and that this dual action is cell type specific. Lavoie et al. [80] report that intracellular zinc chelator influences hippocampal neuronal excitability in rats. The physiological significance of zinc release under excess excitation of zincergic neurons is also examined by an in vivo microdialysis experiment. The increase in extracellular glutamate concentration induced with 100 mM KCl was significantly enhanced in the presence of 1-mM CaEDTA in both the control and zinc-deficient rats [81]. Furthermore, chelation of endogenous zinc by CaEDTA causes a significant increase in ischemic cell death in hippocampal slice cultures [51]. These findings indicate that Zn^{2+} released from zincergic neurons can reduce glutamate release under pathological condition and protect hippocampal cells from the excitotoxicity [44].

Zn^{2+} Signaling under Stressful Condition

Stress disturbs physiological and psychological homeostasis of humans and animals [82]. It activates the HPA system and enhances glucocorticoid secretion from the adrenal cortex (Fig. 3). The hippocampus is enriched with glucocorticoid receptors, plays an important role in stress response [83] and negatively modulates the HPA system activity. However, the hippocampus is vulnerable to stress [84–86] and stress has a profound effect on cognitive function (Fig. 3).

In pathological conditions such as epileptic seizures and ischemia, the extracellular concentrations of both glutamate and zinc are increased in the hippocampus [25, 87, 88]. The extracellular glutamate is also increased in the hippocampus after exposure to novelty stress [89] and tail suspension stress [90], whereas the extracellular zinc is decreased in both cases. The opposite changes in the extracellular concentrations of glutamate and zinc are also observed after treatment with kainate [91] and local electrical stimulation [89]. These data has been obtained by in vivo microdialysis experiments, in which a balance of release and removal determines the concentrations of glutamate and zinc in the extracellular compartment. Although it is unknown why zinc dynamics is diversely changed in the extracellular compartment under stressful and pathological

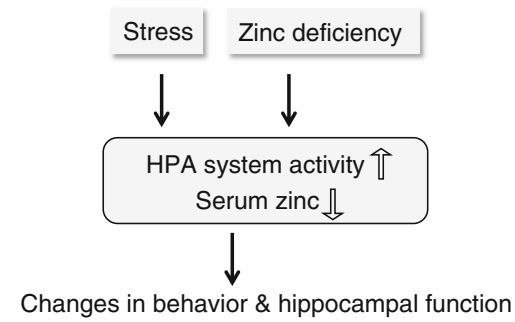

Fig. 3 Influences after exposure to stress and dietary zinc deficiency. Stress and dietary zinc deficiency increase the HPA system activity and decrease serum zinc concentration, followed by the changes in behavior and hippocampal function. It is unclear whether the increase in the HPA system activity occurs earlier than the decrease in serum zinc

conditions, excitation of glutamatergic (zincergic) neurons might be a trigger for zinc dynamics [89, 92].

During excitation of zincergic synapses, Zn^{2+} is taken up into neurons and glial cells via AMPA/kainate receptor activation [45, 47, 92]. Continuous Zn^{2+} influx, which leads to the decrease in extracellular zinc, may attenuate subsequent induction of mossy fiber LTP [90] and NMDA receptor-dependent CA1 LTP, but not that of NMDA receptor-independent CA1 LTP [93]. On the other hand, the block of the decrease in extracellular zinc (continuous zinc influx) in the hippocampus by CaEDTA reduces exploratory activity in a novel environment, which is associated with space recognition [89], suggesting that Zn^{2+} influx into hippocampal cells participates in spatial recognition. In contrast, it is possible that the increase in intracellular Zn^{2+} signaling become a factor to impair learning and memory after exposure to acute stress [90]. Therefore, Zn^{2+} signaling at the synapses may be necessary to be spatiotemporally controlled for zinc-mediated plastic modulation and memory formation.

Zinc Deficiency and Depression

Stress is one of the most potent inhibitors of hippocampal neurogenesis and reduced neurogenesis is thought to relate to pathogenesis of depression [94]. Decreased brain zinc availability reduces hippocampal neurogenesis in mice and rats [95]. It is possible that the decrease in Zn^{2+} signaling is associated with the pathophysiology of depression (Fig. 4). On the other hand, abnormal glucocorticoid secretion induced by stress has been reported in many neuropsychiatric disorders including depression [96–98]. It is thought that exposure to chronic stress precipitates or exacerbates neuropsychiatric disorders (Fig. 4). In human depressives, smaller volumes of the hippocampus are associated with abnormal cortisol secretion [99–101]. Correlations are reported between increases in HPA system activity and depression severity or hippocampal volume loss in human depressives [102]. The hippocampus is a major target of glucocorticoids [103]. This may be a reason of vulnerability of the hippocampus to stress-related disorders. Interestingly, serum zinc concentration is decreased in human depressives [104, 105]. The decrease in serum zinc is normalized by effective antidepressant treatment [106]. Antidepressant therapy can be improved by zinc supplementation [107]. Siwek et al. [108] report that serum zinc is a state marker of depression.

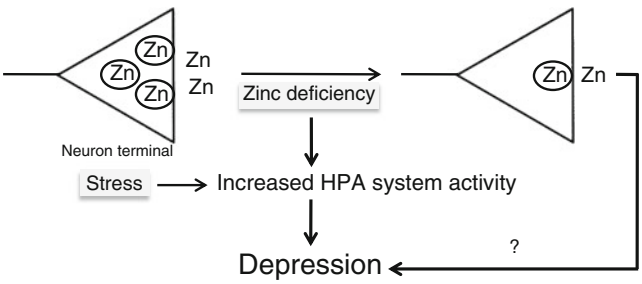

Fig. 4 Increased HPA system activity and depression. Physical and psychological stress, zinc deficiency and aging increase the HPA system activity, which is closely related with the pathogenesis of depression. The relationship between histochemically reactive zinc level and the pathophysiology of depression remains to be solved. Both zinc deficiency and aging, in addition to stress, seem to be risk factors for depression

Dietary zinc deficiency increases serum corticosterone level in mice and rats while decreases serum zinc level [109, 110] (Fig. 3). The increase in depression-like behavior is reported in zinc-deficient mice [111] and rats [112], and is observed in no appreciable decrease in zinc concentration in the brain [113]. Neuropsychological symptoms are caused prior to the decreases in histochemically reactive zinc and/or extracellular zinc in the brain, which are responsive to zinc deficiency [109, 110, 114, 115]. Thus, abnormal corticosterone secretion induced by dietary zinc deficiency may be critical for neuropsychological symptoms such as depression (Fig. 4). Excitability of glutamatergic (zincergic) neurons is changed through the increased secretion of corticosterone under zinc deficiency. Furthermore, this excitability may be potentiated by the decrease in histochemically reactive zinc [34]. Excitability of glutamatergic (zincergic) neurons seems to contribute to more susceptibility to stress in zinc-deficient animals and its related abnormal behavior such as the increase in depression-like behavior [116].

Zinc Homeostasis, the HPA System and Stress Susceptibility in Old Age

Zinc concentration in the brain remains constant in aged animals [117] and humans [8], whereas serum zinc level is significantly lower in aged animals than in young animals [118] and decreases with age in aged humans [37]. Histochemically reactive zinc levels are also lower in aged animals than in adult animals [119, 120]. Judging from the evidence that subclinical zinc deficiency is common in old age, it is possible that histochemically reactive zinc levels are reduced with normal aging in humans [16], as well as chronic dietary zinc deficiency in experimental animals [87, 114, 115] (Fig. 4). The relationship between this reduction in Zn^{2+} signal and depression is an important issue to be solved. On the other hand, serum glucocorticoid concentration is significantly higher in aged animals [121]. The selective increase in the nocturnal levels of cortisol is observed in aged humans [122]. The increase in serum

glucocorticoid level, which is linked to the increased HPA axis activity, might be linked to more susceptibility to stress-related disorders such as depression in aged humans [38].

The increase in the basal Ca^{2+} level and modification of Ca^{2+} signaling in the hippocampal cells are observed in both aged [123, 124] and zinc-deficient [109, 113, 125, 126] animals. Glucocorticoids are associated with these changes in the hippocampus. Repeated corticosterone injections induce anxiety and depression-like behavior in mice and rats [127–129]. Thus, zinc-deficient animals might be useful tools to examine depression.

Perspective

Humans and animals are constantly exposed to environmental stress. Stressful life events are one of the causes of psychiatric disorders and are associated with suicidal behavior [130, 131]. The significance of Zn^{2+} signaling in the brain is poorly understood in comparison with Ca^{2+} signaling. Zn^{2+} signaling is important to maintain healthy brain and its importance is becoming recognized. Zn^{2+} signaling is altered by stress that is associated with all neurological diseases including depression. The responsiveness of the HPA system to zinc deficiency as a stressor indicates the importance of zinc as a nutrient and functional factor. Abnormal glucocorticoid secretion might be induced by the lack of Zn^{2+} signaling in peripheral tissues, which is estimated to be responsive to zinc deficiency. The spatio-temporal analysis on Zn^{2+} signaling is necessary for a better understanding of brain functions.

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