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CALCIUM-DEPENDENT AFTERHYPERPOLARIZATION AND LEARNING IN YOUNG AND AGING HIPPOCAMPUS

John F. Disterhoft[1,3], L.T. Thompson[1,3], James R. Moyer, Jr.[1,3], David J. Mogul[2,3]

[1]Department of Cell and Molecular Biology, [2]Department of Biomedical Engineering and [3]Institute for Neurosciences, Northwestern University, Chicago, IL 60611, USA

Summary

Hippocampally-dependent trace eyeblink conditioning has been shown to be affected by aging. Aging animals take more trials to acquire the association and are more likely to be unable to learn the task. Hippocampal neurons show decreased post-burst afterhyperpolarizations (AHPs) and less accomodation after conditioning, in a time-dependent fashion which may relate to the role of hippocampus in learning consolidation. CA1 neurons in aging rabbits show increased AHPs and more accomodation, i.e., they are less excitable, and larger calcium action potentials. These age-related changes may underlie the learning deficits in aging rabbits. The lipophylic calcium channel blocker nimodipine reduces the AHP, accomodation and calcium action potential at low concentrations in aging but not young CA1 neurons. Nimodipine also enhances learning rate in a variety of tasks, including eyeblink conditioning, in aging but not young animals and humans. Altered calcium handling by neurons of aging mammals is a striking change, is pharmacologically manipulable, and may be an important factor in altered learning and cognitive abilities in the aging.

Key Words: **afterhyperpolarization, calcium, hippocampus, aging**

One of the most troubling concomitants of aging for many individuals is the impairment of learning and memory which often occurs in even "normal" aging. The research program we have been engaged in was designed to explore neuronal changes that occur during aging and contribute to learning deficits, and the role calcium plays in each. An important factor common to both physiological and learning deficits in aging is perturbation of calcium regulation (1,2).

Eyeblink Conditioning: A Model for Studying Aging and the Hippocampus

Eyeblink conditioning is used as a "model system" to analyze neural substrates of learning (3,4) and has many advantages for studying the neurobiology of learning deficits in both aged humans and animals (5,6). It is impaired in both older humans and animals. The changes across the lifespan of rabbits parallel those in humans (7), strengthening its validity as a model system.

Hippocampal lesions in humans and animals cause severe deficits in the ability to transfer information from short- to long-term stores and thus form new memories (8). Despite lesion and recording data showing the importance of the hippocampus for learning (9,10), there has been skepticism about a research strategy using eyeblink conditioning to analyze hippocampal involvement in learning. This skepticism was founded on the demonstration that hippocampectomized rabbits acquire short-delay eyeblink conditioned responses as fast as controls (11). To deal with this issue, we have adopted a hippocampally-dependent trace

paradigm (12,13). In the trace paradigm a blank "trace" period intervenes between CS offset and US onset, which forces the rabbit to form a very short term memory of the CS in order to successfully predict US onset and perform conditioned responses timed properly to avoid the US. We have demonstrated that hippocampally lesioned rabbits cannot acquire the 500 ms trace eyeblink task, even after 2,000 training trials (25 daily training sessions). Control rabbits acquired the task in under 1,000 trials (Fig 1, adapted from 13). Hippocampally lesioned rabbits also exhibited inappropriately timed, "nonadaptive" CRs which occured at too short a blink latency to successfully avoid the airpuff US. Trace eyeblink conditioning taps the hippocampal system's role in forming temporal associations and therefore this structure is necessary for learning this task (10,14). These data support the suggestion that the hippocampus modulates other circuitry, such as the brainstem or cerebellum, in the timing of conditioned responses (15).

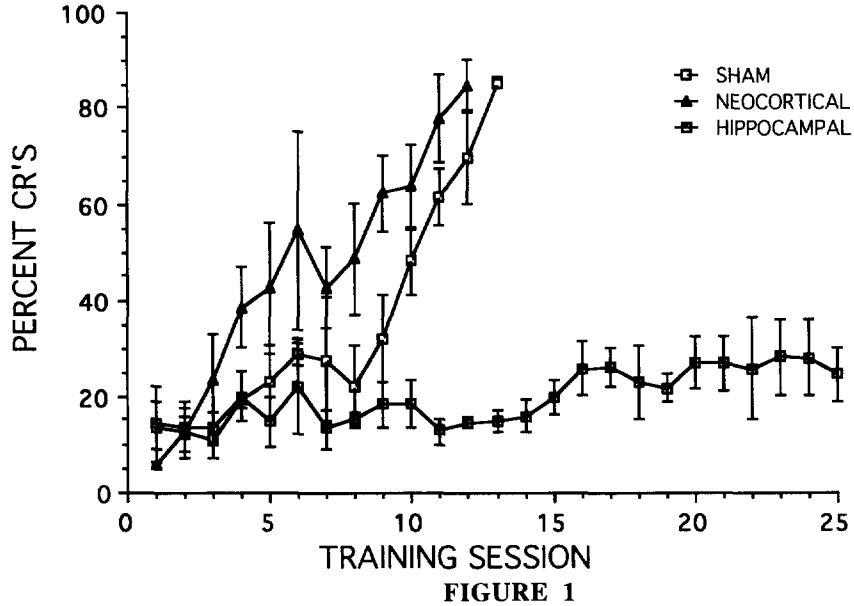

FIGURE 1

Learning curves indicate the deficit in hippocampectomized rabbits was due to a near-total failure to associate the CS and the US.

Use of a hippocampally-mediated learning task is particularly relevant in studies of aging. Many studies have demonstrated structural (16), neurophysiological (17), and neurochemical (18,19) changes in the aging hippocampus. Eyeblink conditioning (5,6) and other hippocampally-dependent tasks such as spatial learning in rats (20,21) are impaired in aged animals.

We have systematically evaluated the development of learning deficits in rabbits across an age range from 6 wk to 36+ mo (22), using the 500 ms trace conditioning task that is sensitive to hippocampal disruption. Beginning at 24 mo rabbits showed a systematic age-related decline in their ability to acquire the trace eyeblink conditioned response. This decline worsened to 30 mo of age and then plateaued. This is a notable impairment as it includes only data from subjects that successfully acquired the task. Additionally, beginning at 24 mo of age, a significant proportion of the total population were severly impaired, i.e., unable to acquire the task at all. This deficit continued to increase with age. By 30 mo, 50% of subjects could not acquire the task; the remaining 50% were impaired compared to younger controls. This is analagous to what is seen in aging humans. With increasing age, a growing percentage of the population has severe difficulty learning the trace eyeblink conditioning task. Thus, this behavioral task serves as a useful preparation for determining neuronal substrates of age-associated learning deficits.

Postsynaptic Excitability Changes in both CA1 and CA3 after Learning

The calcium-dependent post-burst afterhyperpolarization (AHP) which follows a burst of action potentials is reduced in CA1 pyramidal neurons after eyeblink conditioning (23,24). This

reduction increases neuronal excitability and is well correlated with behavioral acquisition. This alteration is localized to the hippocampus, as it occurs in *in vitro* slices separated from their normal afferent and efferent connections (25). It is postsynaptic, as it is evoked by intracellular current injection and persists after block of sodium spike-dependent synaptic transmission (24). We have recently completed analyses of excitability changes in both CA1 and CA3 pyramidal neurons after 500 ms trace eyeblink conditioning (26,27). Membrane excitability changes were studied at time points from 1 h to 14 days after rabbits reached an 80% CR learning criterion. A reduction in the post-burst AHP was observed 1 hr after behavioral acquisition, peaked 24 hr after acquisition, then decayed and returned to a naive-like state within 7 days. Approximately half of CA1 and CA3 neurons showed reduced AHPs after hippocampally-dependent conditioning. Although the neurophysiological properties of CA1 and CA3 pyramidal cells differed markedly, qualitatively similar patterns of learning-dependent changes were observed, as would have been predicted from prior *in vivo* single unit recording data (28,29). We also observed that spike-frequency accommodation was reduced after conditioning in both CA1 and CA3, a finding not seen in our previous *in vitro* studies. It is quite interesting that behavioral retention was essentially asymptotic when examined over the time interval when excitability changes decayed.

Our interpretation of these data is that *postsynaptic excitability changes were maintained in the hippocampus only temporarily*, allowing or supporting cellular alterations in other brain regions for long term or permanent memory storage. In a recent behavioral study consistent with this hypothesis and convergent with our data, rabbits were trace conditioned to criterion and hippocampal lesions made either 24 h or 30 days after training (30). Rabbits lesioned within 24 h of learning were unable to recall the task or to relearn it while those lesioned 30 days after conditioning showed asymptotic retention. These data suggest that the functional changes we observed in the hippocampus are required initially, when the excitability changes are maximal. When the excitability changes return to baseline, the representation of the learned association has shifted to other brain regions, and hippocampal lesions have no effect on retention.

Regulation of Neuronal Excitability in Learning

An important conceptual issue regarding our experimental program should now be addressed directly. When most neuroscientists think about how information is stored in neural networks during learning, changes located at the synapse are considered first. The description of how "Hebb synapses" might change during a hypothetical learning sequence has inspired much work on model systems such as long term potentiation (31). But it should be pointed out that other mechanisms are available for altering synaptic efficacy, e.g., by modulation of excitability at the postsynaptic level (32). Adjustment of cellular excitability could amplify or attenuate synaptic changes occurring in distal dendrites, and affect neuronal firing output after learning.

Our studies defining postsynaptic excitability changes in hippocampal neurons analyzed in slices after eyeblink conditioning offer compelling evidence that calcium-mediated outward potassium currents are reduced in a conditioning-specific fashion to increase hippocampal excitability in learning. Hippocampal pyramidal cells possess slow outward Ca^{2+}-dependent K^+ currents, activated by Ca^{2+} influx into neurons during action potentials. These K^+ currents modulate neuronal firing rates, since they largely determine the resting potential between bursts of spikes. Similar reductions in these or other outward potassium currents are well documented in invertebrate and mammalian learning (33,34,35). The generality of our findings across vertebrate and invertebrate species suggests that postsynaptic modulation of outward potassium currents may be an important conserved mechanism often used to mediate neuronal changes after learning.

Excitability Changes in Aging Hippocampal CA1 Neurons after Conditioning

In addition to studies after learning in young rabbits, we are now analyzing data from a study examining pyramidal neuron excitability in slices from aging rabbits after acquisition of eyeblink conditioning (36). Recall that aging rabbits require many more trials to acquire the task, *if* they are able to acquire it at all (22). We have compared the excitability of CA1 neurons from rabbits who reached behavioral criterion, from rabbits trained for 30 d that never demonstrated more than 30% CRs per session ("dumb bunnies"), and from naive aging rabbits. Both the post-burst AHP and accomodation were reduced in CA1 pyramidal neurons from aging rabbits who

acquired the eyeblink conditioning task. Neurons from aging "dumb bunnies" had excitability levels comparable to aging naive neurons.

Neurons from trained aging rabbits that did not acquire the CR were an additional powerful control, and attest to the behavioral significance of the excitability increases examined *in vitro*. It cannot be argued that a decrease in the AHP was related to presentation of paired trials *per se*. This group of rabbits actually received more paired trials than aging rabbits that acquired the task. But CA1 neurons from the slow group had excitability comparable to those from naive controls. These data further indicate that increased neuronal excitability *in vitro* is correlated with, and may be causally related to, acquisition of the conditioned eyeblink response. Although the post-burst AHP and accomodation were reduced in slices from aging conditioned rabbits as compared to rabbits which did not learn or to naive rabbits, these excitability indices were different from those observed in young trained rabbits. The AHP, though reduced, was larger in neurons from aging trained than young trained rabbits. This difference may directly relate to the slower learning that is characteristic of aging rabbits.

Calcium Currents in Aging and Learning

Calcium influx is increased in aging neurons (37,38). The enhanced depolarizing plateau of the calcium action potential (39) may be sufficient to enlarge and lengthen the calcium-dependent AHP. Our studies have indicated that both the enhanced calcium-dependent afterhyperpolarization (AHP) and the enhanced Ca^{2+} plateau potential in aging neurons are readily blocked by nimodipine, suggesting that influx through L-type calcium channels is enhanced in aging neurons. Thibault *et al.* (40) demonstrated repolarization openings in single L-type channel recordings that they suggested could underly the enhanced plateau potentials and AHPs in aging hippocampal neurons. It is important to note another possibility which has not been investigated thusfar, that other calcium channel types besides L-type may also be changed in aging. Definition of the specific type(s) of channel(s) involved is an obvious next step in defining the cellular and molecular mechanisms for the changes occurring in aging neurons.

We presently have no knowledge of whether calcium currents are altered in hippocampal neurons after associative learning. Preliminary data showed that calcium spike amplitudes were unchanged in trained young adult CA1 neurons recorded in brain slices (24). An interesting, and as yet unexplored, increase was observed in the amount of current required to activate calcium spikes in cells from these conditioned rabbits. Learning-related changes in gating might be more marked in neurons from aging animals.

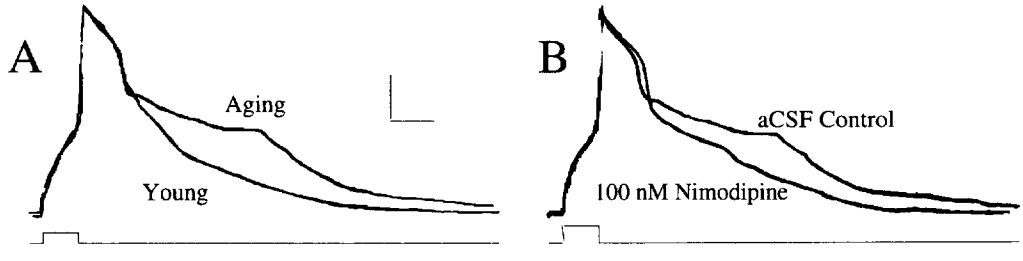

FIGURE 2

A. Calcium action potentials enlarged in aging CA1 & **B.** Reduced by 100 nM nimodipine.

A series of experiments examined the effect of nimodipine on the Ca^{2+} action potential of CA1 pyramidal neurons in hippocampal slices from young and aging rabbits (39). The Ca^{2+} action potential was significantly larger in aging than young CA1 pyramidal neurons. The initial fast phase of the Ca^{2+} action potential was unchanged while the slower, plateau phase was both larger in amplitude and longer in duration in aging as compared to young CA1 neurons (Figure 2A). Since the slow AHP is dependent upon Ca^{2+} influx for its activation, enhancement of the slow Ca^{2+} action potential is consistent with enhancement of the slow AHP.

Nimodipine at high concentrations (10 μM) reduced the slow plateau phase of the Ca^{2+} action potential in both young and aging CA1 neurons, with a greater effect on aging neurons. The plateau phase of the calcium action potential was reduced, but only in aging neurons, by nimodipine at concentrations as low as 100 nM (Figure 2B). Thus, a significant portion of the enhanced Ca^{2+} influx in aging neurons was selectively blocked by nimodipine. The L-type calcium channel blocker, nimodipine, was effective in reducing the majority of the aging-enhanced plateau potential. Our data suggest that alterations in Ca^{2+} flux through the L-type channel are important consequences of the aging process.

Calcium Currents in Acutely Dissociated Hippocampal Neurons

The kinetic and pharmacologic properties of high-threshold, non-inactivating (L-type) Ca^{2+} currents were studied in guinea pig hippocampal pyramidal cells (41). Whole-cell voltage-clamp recordings were obtained from CA1 neurons after dissociation. In order to manipulate Ca^{2+} currents, dihydropyridines were pressure-ejected from pipettes placed near the cell. 10 μM nimodipine (antagonist) reduced the peak whole-cell current by about 35%, while 10 μM BAY-K-8644 (agonist) potentiated the current by an approximately equal amount. These effects were reversible after washing. Thus, when applied directly to the soma of dissociated CA1 neurons under good voltage control, nimodipine blocked L-type Ca^{2+} currents. L-type currents accounted for a sizable fraction of the whole-cell Ca^{2+} current, but not the entire current.

Healthy, viable pyramidal neurons have also been successfully dissociated from the rabbit hippocampus in other work. In our first series of experiments, Ba^{2+} current through voltage-dependent calcium channels was used to demonstrate both low-threshold T- and high-threshold L-type Ca^{2+} currents. Ca^{2+}-activated K^+ currents were examined by a two-pulse protocol that explored the effect of the prepulse level for elicitation of a Ca^{2+} current prior to recording any outward potassium current. A significant outward current was elicited only when a large inward Ca^{2+} current was generated by the prepulse, indicating the existence of Ca^{2+}-activated K^+ currents in these cells. The tail-current was large. These experiments are being extended in young and aging neurons acutely dissociated from rabbit hippocampus.

Ca^{2+}-activated K^+ Currents in Aging

The calcium-dependent slow AHP in CA1 neurons in hippocampal slices from aging (36+ mo) rabbits was considerably larger both in amplitude and in total area, representing a significant enhancement of the AHP in aging neurons (38). This increase, which makes CA1 neurons less excitable, may impair the ability of the hippocampal circuitry to form new memories in aging animals (37). As further evidence for reduced excitability, aging CA1 neurons showed considerably more spike frequency accomodation to a long depolarizing pulse than did cells from younger rabbits. Bath application of nimodipine at high concentrations (10 μM) reduced the AHP and accomodation in young and aging neurons, with greater magnitude effects on aging neurons (38). When more physiologically reasonable concentrations of the calicum antagonist were used, a striking differential effect was observed. At concentrations as low as 100 nM, nimodipine reduced the amplitude and duration of the slow AHP in aging but not in young neurons. Nimodipine reduced the AHP of aging neurons into the range observed in untreated young neurons. The effects of nimodipine on accomodation were similar. High concentrations (> 1.0 μM) reduced accomodation in both young and aging neurons, while at lower concentrations (10 nM) effects were seen only in aging neurons. This age-dependent differentiatial effect on hippocampal neurons was similar to that observed *in vivo* (42).

The relevance of AHP reductions during learning in young adults to learning deficits in aging animals may be rather direct. Increased calcium levels in aging neurons would lead to larger post-burst afterhyperpolarizations, potentials which reflect the action of a calcium-dependent outward potassium current. Such aging-related changes in a calcium-mediated process would be predicted by the "calcium hypothesis of aging" (1). Landfield and Pitler (37) demonstrated that the AHP is prolonged in hippocampal CA1 neurons from aged rats, thus making them less excitable. They suggested that this increase was a causative factor in learning impairments in aging. The AHP from aging rabbit CA1 neurons was enhanced both in amplitude and duration; spike frequency accomodation was also increased (38). We hypothesized that

calcium channel blockers might reduce the effect of aging on hippocampal neuron excitability and therefore might also facilitate learning by aging rabbits.

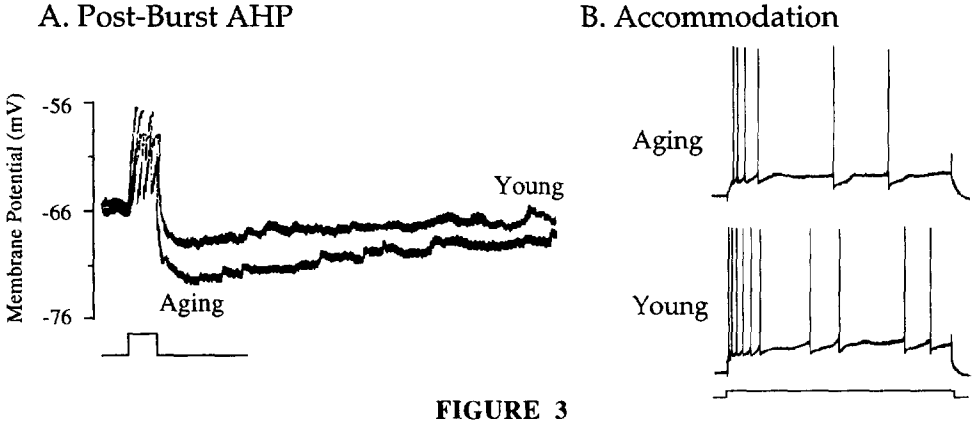

FIGURE 3
A. Post-burst AHP & **B.** Accomodation are Increased in Aging CA1 Neurons

Effect of Ca^{2+} Antagonists on Learning

Nimodipine, which blocks neuronal L-type channels (43) and readily crosses the blood brain barrier (44), was tested on trace eyeblink conditioning in young (3 mo) and aging (36+ mo) rabbits. Nimodipine infused intravenously at a rate of 1 μg/kg/min during training facilitated acquisition of the trace eyeblink conditioned response in aging rabbits (45). In fact, treated aging rabbits reached a criterion of 8 CRs in 10 trials faster than did young animals receiving nimodipine or than young controls. Aging controls took much longer to reach criterion than young controls. Pseudoconditioned nimodipine-treated controls showed no nonspecific sensitization to sensory stimuli. There was also no difference in the amplitude or latency of conditioned or unconditioned responses between treated and control groups. The behavioral data suggested that nimodipine enhanced neural functions required to form associations between stimuli, and supported our initial hypothesis. Nimodipine added to the food supply of aging rabbits (860 ppm for 1 mo) also enhanced acquisition rates in trace conditioning (46). The enhancement was not as dramatic with oral administration, possibly because serum and brain nimodipine levels were not elevated as much as by i.v. application. To further clarify these relationships, we next carried out an i.v. dose-response study of the effects of calcium channel blockade on learning in aging rabbits, measuring serum and brain nimodipine concentrations (47). Doses above a threshold of 0.5 μg/kg/min were effective with facilitation maximal at 1 μg/kg/min. Learning rate did not increase at higher doses. The concentration of nimodipine in plasma also increased dose-dependently, with effective serum concentrations distributed between 10-50 ng/ml. Concentrations above 50 ng/ml did not further enhance acquisition. Nimodipine, of course, is not the only calcium channel antagonist that may have effects in aging. Rather, we have used it as a tool to specifically block L-type Ca^{2+} influx.

Our working hypothesis is that behavioral effects were largely mediated by the blockade of Ca^{2+} entry into neurons via L-type channels, via reductions in the Ca^{2+}-dependent AHP. Nimodipine also enhances cerebral blood flow by dilating blood vessels. Our data addressed the issue of increased blood flow, as i.v. nimodipine at a dose of 0.1 μg/kg/min increases cerebral blood flow in rabbits as much as two-fold (48) but had no effect on learning rates. In addition, we found that this concentration of nimodipine had no effect on CA1 pyramidal neuron activity *in vivo* in aging or young rabbits (42). While neither piece of data rules out blood flow-dependent effects, they certainly do not offer evidence in support of such effects mediating learning enhancement. The concentrations of nimodipine which reduced the post-burst AHP and accomodation in aging CA1 neurons *in vitro* (38,39) are comparable to those calculated to be present in the extracellular space in the hippocampus when 1 μg/kg/min intravenous nimodipine was given (Krause, personal communication). This dose gave maximal behavioral effects (45,47) and maximally enhanced CA1 firing rates in conscious rabbits (42). All effects were observed at low concentrations in aging, but not young, rabbits. The effects on aging neurons *in*

vitro cannot have been mediated by altered blood flow, a further indication that the *in vivo* learning enhancements were likely an effect of nimodipine's actions on neurons.

We have done several studies of human eyeblink conditioning. In a clinical trial, oral nimodipine was administered to normal young (20-30 yr) or aging (60-75 yr) subjects for 3 mo (49). Improved conditioning was seen in aging subjects 1 mo after treatment began. The effect increased and was statistically significant after 3 mo. Subgroup analyses showed that those aging individuals with the poorest eyeblink conditioning before treatment exhibited the largest benefit from nimodipine. To our knowledge, this is the first time that the same behavioral task has been similarly enhanced by drug treatment in both an animal and a human model.

Finally, aging rabbits that received oral nimodipine (46) were evaluated for their performance in an "open field" (50). Young rabbits in the open field tended to stay next to the walls, did not explore much, and spent considerable time observing their environment. Aging control rabbits wandered aimlessly around the open field, exposed themselves in the center, and moved around a lot, which would make them easy prey in the wild. Aging nimodipine-treated rabbits, on the other hand, behaved very much like young controls. The open field tests general cognitive functioning and awareness of the rabbit to its surroundings and its level of alertness.

In summary, nimodipine markedly facilitated acquisition of the trace eyeblink conditioned response in aging rabbits (45,46,47) and humans (49); improved sensorimotor behaviors in aging rats (51); reversed open field deficits in aging rabbits (50); improved delayed matching-to-sample performance in aging primates (52); and improved spatial learning in aging rats (53,54). The often dramatic behavioral effects of calcium antagonists in aging animals suggest that research focusing on calcium influx as well as calcium's effects on potassium channels are fruitful avenues for understanding important cellular mechanisms for changes in aging neurons that affect and impair learning. Our observations that Ca^{2+} channel antagonists reduce the post-burst afterhyperpolarization (AHP) and decrease accommodation in aging neurons, and also enhance learning, warrant further investigation of specific mechanisms mediating these changes.

Acknowledgements

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