Advances in Social Sciences 社会科学前沿, 2023, 12(4), 1778-1785
Published Online April 2023 in Hans. https://www.hanspub.org/journal/ass
https://doi.org/10.12677/ass.2023.124242

Hans汉斯

经颅直流电刺激延缓情景记忆老化的微观机制

李朝会

西南大学心理学部，重庆

收稿日期：2023年2月19日；录用日期：2023年4月11日；发布日期：2023年4月21日

摘　要

情景记忆是受老化影响最严重的长期记忆。经颅直流电刺激可以延缓情景记忆老化，并且有研究对其干预机制做出初步探讨，但尚未有研究进行系统梳理。本文基于情景记忆老化的神经生物学基础研究，从微观层面对经颅直流电刺激的干预机制进行探讨。在微观(分子、细胞)水平，经颅直流电刺激通过诱导膜电位变化、调节神经递质系统以及脑源性神经营养因子来影响突触可塑性，从而延缓情景记忆的老化。

关键词

情景记忆，经颅直流电刺激，老化，干预，神经递质

Mechanism of Transcranial Direct Current Stimulation Reducing Episodic Memory Aging

Chaohui Li

Faculty of Psychology, Southwest University, Chongqing

Received: Feb. 19th, 2023; accepted: Apr. 11th, 2023; published: Apr. 21st, 2023

Abstract

Episodic memory is the long-term memory most affected by aging. Transcranial direct current stimulation can delay episodic memory aging, and its intervention mechanism has been preliminarily discussed. Based on the basic neurobiological research of episodic memory aging, this paper discusses the intervention mechanism of transcranial direct current stimulation from the mi-

文章引用: 李朝会. 经颅直流电刺激延缓情景记忆老化的微观机制[J]. 社会科学前沿, 2023, 12(4): 1778-1785.
DOI: 10.12677/ass.2023.124242

cro level. At the microscopic (molecular, cellular) level, transcranial direct current stimulation affects synaptic plasticity by inducing changes in membrane potential, modulating neurotransmitter systems, and brain-derived neurotrophic factors, thereby delaying episodic memory aging.

Keywords

Episodic Memory, Transcranial Direct Current Stimulation, Aging, Intervention, Neurotransmitter

1. 引言

情景记忆(Episodic Memory)包含了何时何地发生了何事等一些详细信息，是个体对生活事件的记忆[1]。情景记忆是受年龄影响最大的长期记忆[2]。因此对情景记忆老化进行干预变得尤为重要。以往大量研究表明，tDCS 改善了健康老年人情景记忆表现[3] [4] [5] [6]。理解行为背后的机制有利于研究者建立理论模型，并为制定更为有效的干预方案提供依据。已有研究对 tDCS 延缓情景记忆老化的微观机制做出初步探讨，但尚未有研究对其干预机制进行系统梳理。

本文基于情景记忆老化相关的神经生物学基础，从微观和水平对 tDCS 的干预机制加以探讨。在微观(分子、细胞)水平，突触可塑性是记忆的神经生理基础[7]。老化会导致神经递质、相关受体以及脑源性神经营养因子功能失调，进而损伤突触可塑性，导致记忆功能受损。tDCS 可以通过诱导膜电位变化、调节神经递质系统以及脑源性神经营养因子来影响突触可塑性，从而延缓情景记忆老化。

2. 情景记忆老化的微观机制

情景记忆老化涉及神经元兴奋性降低[8]、神经递质失调[9]、受体表达性降低[10]、脑源性神经营养因子以及神经调质失调[11] [12]，上述变化都会影响突触可塑性，进而损害记忆功能。

2.1. 氨基酸类神经递质

氨基酸类神经递质中包含兴奋性神经递质谷氨酸(Glutamate, Glu)和抑制性神经递质 γ 氨基丁酸(Gamma Aminobutyric Acid, GABA)，它们以多种形式影响记忆功能[13]。具体来讲，谷氨酸可以诱导神经元去极化、调节突触可塑性[14]，并参与长时程增强过程[15]。海马 GABA 水平与记忆提取表现显著相关[16]，GABA 含量增加对记忆有负面影响[17]。GABA 系统失调可能是情景记忆病理性衰退的早期标志物[18]。不同类型的神经递质通过与受体结合来调节突触可塑性，进而调节学习记忆能力[19]。谷氨酸受体包括 α-氨基-3-羟基-5-甲基 4-异噁恶唑丙酸(α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid, AMPA)和 N-甲基-M 天冬氨酸(N-methyI-D-aspartate, NMDA)，二者分别参与细胞去极化期间钠离子和钙离子的流入，并且 NMDA 受体产生延长的动作电位，与诱导长时程增强作用有关。随着年龄增长，观察到 NMDA 受体功能衰退[10]，并且海马中谷氨酸能神经传递也出现年龄相关的下降，这可能是由 NMDA 受体介导的[9]。

2.2. 单胺类类神经递质

包括多巴胺、血清素、去甲肾上腺素在内的单胺类神经递质系统和乙酰胆碱系统出现年龄相关的失

调，该变化与记忆功能受损有关。上述物质也被称作神经调质，主要是通过浓度变化和受体亚型依赖性对突触可塑性产生影响。首先，适量的多巴胺可以调节突触活动[20]、诱导长时程增强作用，从而改善记忆表现[21]。与年轻人相比，老年人多个脑区的多巴胺含量出现年龄相关的下降[22]，导致长时程增强作用受损，这或许与多巴胺受体亚型 D1 和 D2 的老化有关[23]。其次，去甲肾上腺激素可以调节突触可塑性，诱导长时程增强作用，进而改善记忆表现。记忆能力随年龄下降，并且该变化和去甲肾上腺素减少有关[24]。动物研究表明，外源性注射去甲肾上腺素可以增强老年大鼠的 AMPA 运输，进而改善长时程增强作用[25]。再次，适量的 5-羟色胺可以直接激活不同的受体，也可以通过调节谷氨酸能、多巴胺能等其他神经传递系统，间接地调节突触可塑性，进而改善学习和记忆[19]。老化过程中，老年人多个脑区的 5-羟色胺含量降低[26]，并且该变化和记忆功能下降有关[27]。最后，胆碱能系统的完整性与老年人情景记忆功能的个体差异有关[28]。乙酰胆碱主要通过激活毒蕈碱(Muscarinic) M1 受体来促进海马长时程增强作用[29]。它可以直接与突触后受体结合，也可以和神经胶质细胞受体结合，减少炎症并促进 BDNF 等生长因子的释放。此外，乙酰胆碱也可以通过抑制小胶质细胞的过度激活来减少记忆损害[30]。随年龄增长，乙酰胆碱系统的完整性下降[31]，这与年龄相关的记忆功能受损有关[32]。

2.3. 脑源性神经营养因子

在老化进程中，脑源性神经营养因子(Brain Derived Neurotrophic Factor, BDNF)浓度失调，导致记忆功能受损。首先，BDNF 对神经元和神经胶质的发育、保护以及突触可塑性非常重要[33]，正常含量的 BDNF 会促进学习和记忆。BDNF 浓度失调会破坏兴奋性与抑制性神经递质之间的平衡，从而损害记忆功能。这可能是因为，BDNF 与原肌球蛋白相关激酶 B (Tropomyosin-Related Kinase B, TrkB)传输信号的下降引起了小胶质细胞的过度激活，从而导致年龄相关的神经退行性疾病[11]。此外，BDNF 也可以通过调节贩运和 NMDA 受体的表达水平来调节突触可塑性。具体来说，BDNF 通过调节 NMDA 受体的磷酸化来增强谷氨酸能突触传递，进而增强 NMDA 受体的活性[34]。如前所述，NMDA 受体产生延长的动作电位，与诱导长时程增强作用有关。随年龄增长，BDNF 浓度降低，该变化与记忆受损有关[35]。

3. tDCS 延缓情景记忆老化的微观机制

在微观(分子、细胞)水平，tDCS 可以通过诱导膜电位变化，调节记忆相关的神经递质、以及非神经元物质(神经胶质、脑源性神经营养因子)来影响神经可塑性，进而延缓老年人情景记忆衰退。如图 1 所示。

3.1. tDCS 诱导膜电位变化

tDCS 或许可以诱导膜电位变化，继而影响神经递质的释放，从而调节突触可塑性，改善记忆表现。tDCS 可以在皮层表面区域产生显著的电流，并在不诱发动作电位的情况下影响神经元的兴奋性[36] [37]，这主要是通过使静息膜电位的极化来实现的。具体来讲，阳极 tDCS 会产生和膜电位一致的电场，使得产生动作电位所需的电势差变小，即降低了产生动作电位的阈值，从而增加静息膜电位的兴奋性。不过钙离子和钠离子通道阻滞剂会消除阳极刺激的作用[38]，说明该过程受到电压门控离子通道的介导。阴极与之相反，起到抑制兴奋性的作用[39]。具体来说，tDCS 使得静息膜电位超极化，从而导致相关电压门控的失活[38]。神经递质的释放依赖于细胞内电压，细胞去极化会导致钙内流，进而促进神经递质释放。当神经递质与突触后受体结合后，就会产生兴奋性或抑制性反应。因此可以推测，tDCS 诱导膜电位变化，进而调节神经递质释放是 tDCS 延缓情景记忆老化的微观作用途径之一。

3.2. tDCS 对神经递质系统的影响

tDCS 或许可以通过调节兴奋性和抑制性神经递质的平衡来影响突触可塑性，进而影响记忆表现。首

先，有研究发现，在 tDCS 刺激位点下方，谷氨酸和谷氨酰胺组合的水平显著升高[40]，并且在非刺激区域也发现了相应变化[41]。此外，tDCS 可以降低新皮层抑制性神经递质 GABA 的浓度，该变化可以预测随后的任务表现[42]。其次，tDCS 诱导的长期增益可能是因为 tDCS 改变了突触可塑性，进而促进类长时程增强作用[43]。如前所述，NMDA 受体产生延长的动作电位，而受体表达性依赖于细胞内钙离子水平。tDCS 作用期间，钙通道活性发生了变化，这一变化有助于长时程增强作用[44]。也就是说，tDCS 促进了 NMDA 受体表达。此外，GABA 受体激动剂减弱了阳极 tDCS 效果[45]。阳极刺激可以使得皮层中 GABA 的浓度降低[46]，这可能是通过阻断钙通道来减少抑制性神经递质 GABA 的释放，而 GABA 浓度下降也会增强 NMDA 受体功能[38]。此外，tDCS 可以诱导海马 AMPA 受体易位和磷酸化[47]，该变化同样会促进长时程增强作用。因此可以推测，tDCS 通过调节神经递质与神经元膜通道来影响突触可塑性，进而延缓情景记忆老化。

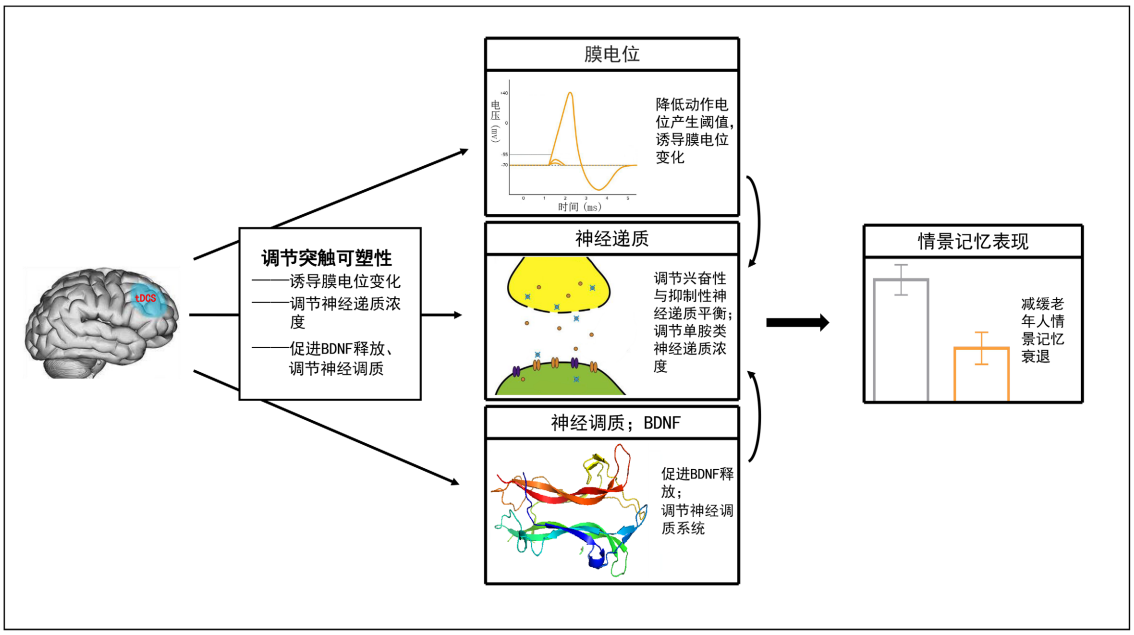

Figure 1. Microscopic mechanism of tDCS delay episodic memory aging
图 1. tDCS 延缓情景记忆老化的微观机制

3.3. tDCS 对神经调质与脑源性神经营养因子的影响

tDCS 可以调节神经调质以及脑源性神经营养因子来间接影响突触可塑性，进而延缓情景记忆老化。首先，tDCS 可以调节 5-羟色胺，多巴胺等单胺类神经递质以及乙酰胆碱浓度。这类神经递质也被称为神经调质，它们广泛地影响着皮层及皮层下区域。具体来讲，tDCS 可以促进多巴胺释放进而调节谷氨酸与谷氨酰胺浓度，提升多个网络内部连接性[48]。血清素可以显著增强 tDCS 的延迟效应的幅度和持续时间[49]。胆碱酯酶抑制剂基本上阻断了由阳极 tDCS 诱导的皮层兴奋性效应[50]，该结果表明了胆碱能在 tDCS 效应中的介导作用。其次，动物研究表明，tDCS 增加了大鼠纹状体中的 BDNF 水平(Leffa *et al*., 2016)。另有研究发现，原肌球蛋白相关激酶 B (Tropomyosin-Related Kinase B, TrkB)抑制剂减弱了 tDCS 诱导的长时程增强作用。这一结果表明 BDNF-TrkB 通路在 tDCS 效应中的重要作用[51]。研究者认为，tDCS 通过提升 BDNF 表达来诱导 LTP 进而提升突触可塑性[52]。因此可以推测，tDCS 通过调节神经调质和 BDNF 来影响神经递质及其受体，进而延缓情景记忆老化。

综上，情景记忆老化与微观(分子、细胞)水平的各种变化有关。在微观水平，突触可塑性是记忆的生理基础。神经递质、脑源性神经营养因子、神经胶质随年龄发生的变化会影响突触可塑性。tDCS 通过改变神经元的兴奋性、调节神经递质、神经调质系统以及脑源性神经营养因子水平，改善突触可塑性，从而延缓情景记忆老化。

4. 总结与展望

本文基于情景记忆老化相关的神经生物学基础，从微观(分子、细胞)水平分析了 tDCS 对情景记忆老化的干预机制。在微观水平，情景记忆老化与神经元兴奋性降低、神经递质失调、受体表达性降低、脑源性神经营养因子和神经调质失调有关。tDCS 可以通过诱导膜电位极化、影响神经递质、脑源性神经营养因子以及神经调质来改善神经元可塑性，进而延缓情景记忆老化。总而言之，tDCS 在延缓情景记忆老化的微观机制研究方面取得了一定成果，但仍然存在一些尚待解决的问题和需进一步完善之处，未来研究可以针对以下几个方面进行深入探讨：

第一，进一步探讨 tDCS 诱导的微观和宏观水平变化的联系。从神经化学视角出发来考虑神经机制能够阐明认知功能(如注意和记忆)之间的关系[53]。已有研究发现局部 GABA 水平和网络连接之间呈反比关系[54]。此外多巴胺信号可以调节大脑网络内部的稳定性[55]，并且神经调节系统有助于大脑功能分离和整合之间转变[56]。计算模型认为，年龄相关的多巴胺能失调与神经去分化有关[57] [58]，即，神经调质失调导致神经元信噪比降低，进而导致神经表征降低[59]。未来研究可以深入探讨 tDCS 诱导的微观与宏观之间的关系，这将有助于研究者更好的理解相应的干预机制。

第二，探究神经胶质细胞是否是 tDCS 延缓情景记忆老化的中介因素。神经胶质细胞负责神经回路的保护，再生和重塑，它与神经元、其他神经胶质细胞以及老化相关的免疫细胞进行广泛的交互[60]，并且对记忆的编码和巩固起着至关重要的作用[61] [62]。星形胶质细胞和小胶质细胞是两种较为重要的神经胶质细胞，它们在脑发育过程中起到互补的作用[63]。星形胶质细胞通过释放神经营养因子保护突触[64]，有助于突触和神经元环境稳态[65]。小胶质细胞充当吞噬细胞，释放神经营养因子和调节细胞因子来保护神经元[66] [67]。在老年人中，神经胶质细胞出现功能性丧失，使得神经组织的防御和再生能力下降[12]，进而损害记忆功能。神经胶质细胞无法产生动作电位，但是对于电压变化非常敏感，其中可能包括外部电刺激。理论上，tDCS 可以影响神经胶质的跨膜电位，从而调节神经递质的平衡[68]。也就是说，tDCS 的作用可能不仅限于神经细胞，也可能通过影响神经胶质来间接调节突触可塑性，进而延缓情景老化。目前，tDCS 对神经胶质的影响的证据仍然很少，未来研究可以考虑在此方向做进一步探索。

参考文献

[1] Tulving, E. (1983) Elements of Episodic Memory. Oxford University Press, Oxford.

[2] Rönnlund, M., Nyberg, L., Bäckman, L., & Nilsson, L.-G. (2005) Stability, Growth, and Decline in Adult Life Span Development of Declarative Memory: Cross-Sectional and Longitudinal Data from a Population-Based Study. *Psychology and Aging*, **20**, 3-18. https://doi.org/10.1037/0882-7974.20.1.3

[3] Antonenko, D., *et al*. (2018) Neuronal and Behavioral Effects of Multi-Day Brain Stimulation and Memory Training. *Neurobiology of Aging*, **61**, 245-254. https://doi.org/10.1016/j.neurobiolaging.2017.09.017

[4] Flöel, A., *et al*. (2012) Non-Invasive Brain Stimulation Improves Object-Location Learning in the Elderly. *Neurobiology of Aging*, **33**, 1682-1689. https://doi.org/10.1016/j.neurobiolaging.2011.05.007

[5] Crossman, M., Bartl, G., Soerum, R. and Sandrini, M. (2019) Effects of Transcranial Direct Current Stimulation over the Posterior Parietal Cortex on Episodic Memory Reconsolidation. *Cortex*, **121**, 78-88. https://doi.org/10.1016/j.cortex.2019.08.009

[6] Friehs, M.A., Greene, C. and Pastötter, B. (2021) Transcranial Direct Current Stimulation Over the Left Anterior Temporal Lobe During Memory Retrieval Differentially Affects True and False Recognition in the DRM Task. *European Journal of Neuroscience*, **54**, 4609-4620. https://doi.org/10.1111/ejn.15337

[7] Malinow, R. and Malenka, R.C. (2002) AMPA Receptor Trafficking and Synaptic Plasticity. *Annual Review of Neuroscience*, **25**, 103-126. https://doi.org/10.1146/annurev.neuro.25.112701.142758

[8] Moyer, J.R., Power, J.M., Thompson, L.T. and Disterhoft, J.F. (2000) Increased Excitability of Aged Rabbit CA1 Neurons after Trace Eyeblink Conditioning. *Journal of Neuroscience*, **20**, 5476-5482. https://doi.org/10.1523/JNEUROSCI.20-14-05476.2000

[9] Kumar, A. and Foster, T.C. (2019) Alteration in NMDA Receptor Mediated Glutamatergic Neurotransmission in the Hippocampus During Senescence. *Neurochemical Research*, **44**, 38-48. https://doi.org/10.1007/s11064-018-2634-4

[10] Foster, T., Kyritsopoulos, C. and Kumar, A. (2017) Central Role for NMDA Receptors in Redox Mediated Impairment of Synaptic Function During Aging and Alzheimer's Disease. *Behavioural Brain Research*, **322**, 223-232. https://doi.org/10.1016/j.bbr.2016.05.012

[11] Wu, S.-Y., *et al*. (2020) BDNF Reverses Aging-Related Microglial Activation. *Journal of Neuroinflammation*, **17**, Article No. 210. https://doi.org/10.1186/s12974-020-01887-1

[12] Verkhratsky, A., Zorec, R., Rodriguez-Arellano, J.J. and Parpura, V. (2019) Neuroglia in Ageing. In: Verkhratsky, A., Ho, M., Zorec, R. and Parpura, V., Eds., *Neuroglia in Neurodegenerative Diseases*. *Advances in Experimental Medicine and Biology*, Vol 1175, Springer, Singapore, 181-197. https://doi.org/10.1007/978-981-13-9913-8_8

[13] Herz, J., *et al*. (2021) GABAergic Neuronal IL-4R Mediates T Cell Effect on Memory. *Neuron*, **109**, 3609-3618. https://doi.org/10.1016/j.neuron.2021.10.022

[14] Salinska, E. and Stafiej, A. (2003) Metabotropic Glutamate Receptors (mGluRs) Are Involved in Early Phase of Memory Formation: Possible Role of Modulation of Glutamate Release. *Neurochemistry International*, **43**, 469-474. https://doi.org/10.1016/S0197-0186(03)00036-6

[15] 赵永才, 吴耿安, 黄亨奋. 运动与记忆: N-甲基-D-天冬氨酸受体和谷氨酸在学习记忆中的作用[J]. 中国临床康复, 2005, 9(37): 101-103.

[16] Spurny, B., *et al*. (2020) Hippocampal GABA Levels Correlate with Retrieval Performance in an Associative Learning Paradigm. *NeuroImage*, **204**, Article ID: 116244. https://doi.org/10.1016/j.neuroimage.2019.116244

[17] Farr, S.A., Uezu, K., Creonte, T.A., Flood, J.F. and Morley, J.E. (2000) Modulation of Memory Processing in the Cingulate Cortex of Mice. *Pharmacology Biochemistry and Behavior*, **65**, 363-368. https://doi.org/10.1016/S0091-3057(99)00226-9

[18] Jiménez-Balado, J. and Eich, T.S. (2021) GABAergic Dysfunction, Neural Network Hyperactivity and Memory Impairments in Human Aging and Alzheimer's Disease. *Seminars in Cell & Developmental Biology*, **116**, 146-159. https://doi.org/10.1016/j.semcdb.2021.01.005

[19] 李佳琪, 高丽, 周玉枝, 秦雪梅, 杜冠华. 衰老性学习记忆减退相关的脑内单胺类神经递质研究进展[J]. 药学学报, 2017, 52(11): 1639-1646.

[20] Monte-Silva, K., *et al*. (2009) Dose-Dependent Inverted U-Shaped Effect of Dopamine (D_2-Like) Receptor Activation on Focal and Nonfocal Plasticity in Humans. *Journal of Neuroscience*, **29**, 6124-6131. https://doi.org/10.1523/JNEUROSCI.0728-09.2009

[21] Thirugnanasambandam, N., Grundey, J., Paulus, W. and Nitsche, M.A. (2011) Dose-Dependent Nonlinear Effect of $_L$-DOPA on Paired Associative Stimulation-Induced Neuroplasticity in Humans. *Journal of Neuroscience*, **31**, 5294-5299. https://doi.org/10.1523/JNEUROSCI.6258-10.2011

[22] Seaman, K.L., *et al*. (2019) Differential Regional Decline in Dopamine Receptor Availability across Adulthood: Linear and Nonlinear Effects of Age. *Human Brain Mapping*, **40**, 3125-3138. https://doi.org/10.1002/hbm.24585

[23] Karrer, T.M., Josef, A.K., Mata, R., Morris, E.D. and Samanez-Larkin, G.R. (2017) Reduced Dopamine Receptors and Transporters but Not Synthesis Capacity in Normal Aging Adults: A Meta-Analysis. *Neurobiology of Aging*, **57**, 36-46. https://doi.org/10.1016/j.neurobiolaging.2017.05.006

[24] Mei, Y., *et al*. (2015) Aging-Associated Formaldehyde-Induced Norepinephrine Deficiency Contributes to Age-Related Memory Decline. *Aging Cell*, **14**, 659-668. https://doi.org/10.1111/acel.12345

[25] Luo, Y., *et al*. (2015) Reversal of Aging-Related Emotional Memory Deficits by Norepinephrine via Regulating the Stability of Surface AMPA Receptors. *Aging Cell*, **14**, 170-179. https://doi.org/10.1111/acel.12282

[26] Haider, S., *et al*. (2014) Age-Related Learning and Memory Deficits in Rats: Role of Altered Brain Neurotransmitters, Acetylcholinesterase Activity and Changes in Antioxidant Defense System. *AGE*, **36**, 1291-1302. https://doi.org/10.1007/s11357-014-9653-0

[27] Saleem, S., Tabassum, S., Ahmed, S., Perveen, T. and Haider, S. (2014) Senescence Related Alteration in Hippocampal Biogenic Amines Produces Neuropsychological Deficits in Rats. *Pakistan Journal of Pharmaceutical Sciences*, **27**, 837-845.

[28] Richter, N., *et al*. (2014) The Integrity of the Cholinergic System Determines Memory Performance in Healthy Elderly. *NeuroImage*, **100**, 481-488. https://doi.org/10.1016/j.neuroimage.2014.06.031

[29] Dennis, S.H., *et al*. (2016) Activation of Muscarinic M1 Acetylcholine Receptors Induces Long-Term Potentiation in the Hippocampus. *Cerebral Cortex*, **26**, 414-426. https://doi.org/10.1093/cercor/bhv227

[30] Maurer, S.V. and Williams, C.L. (2017) The Cholinergic System Modulates Memory and Hippocampal Plasticity *via* Its Interactions with Non-Neuronal Cells. *Frontiers in Immunology*, **8**, Article 1489. https://doi.org/10.3389/fimmu.2017.01489

[31] Mitsis, E.M., *et al*. (2009) Age-Related Decline in Nicotinic Receptor Availability with [^{123}I]5-IA-85380 SPECT. *Neurobiology of Aging*, **30**, 1490-1497. https://doi.org/10.1016/j.neurobiolaging.2007.12.008

[32] Preston, A.R. and Eichenbaum, H. (2013) Interplay of Hippocampus and Prefrontal Cortex in Memory. *Current Biology*, **23**, R764-R773. https://doi.org/10.1016/j.cub.2013.05.041

[33] Kowiański, P., *et al*. (2018) BDNF: A Key Factor with Multipotent Impact on Brain Signaling and Synaptic Plasticity. *Cellular and Molecular Neurobiology*, **38**, 579-593. https://doi.org/10.1007/s10571-017-0510-4

[34] Caldeira, M.V., *et al*. (2007) BDNF Regulates the Expression and Traffic of NMDA Receptors in Cultured Hippocampal Neurons. *Molecular and Cellular Neuroscience*, **35**, 208-219. https://doi.org/10.1016/j.mcn.2007.02.019

[35] Mizoguchi, Y., Yao, H., Imamura, Y., Hashimoto, M. and Monji, A. (2020) Lower Brain-Derived Neurotrophic Factor Levels Are Associated with Age-Related Memory Impairment in Community-Dwelling Older Adults: The Sefuri Study. *Scientific Reports*, **10**, Article No. 16442. https://doi.org/10.1038/s41598-020-73576-1

[36] Liu, A., *et al*. (2018) Immediate Neurophysiological Effects of Transcranial Electrical Stimulation. *Nature Communications*, **9**, Article No. 5092. https://doi.org/10.1038/s41467-018-07233-7

[37] Reed, T. and Kadosh, R.C. (2018) Transcranial Electrical Stimulation (tES) Mechanisms and Its Effects on Cortical Excitability and Connectivity. *Journal of Inherited Metabolic Disease*, **41**, 1123-1130. https://doi.org/10.1007/s10545-018-0181-4

[38] Nitsche, M.A., *et al*. (2003) Pharmacological Modulation of Cortical Excitability Shifts Induced by Transcranial Direct Current Stimulation in Humans. *The Journal of Physiology*, **553**, 293-301. https://doi.org/10.1113/jphysiol.2003.049916

[39] Woods, A.J., *et al*. (2016) A Technical Guide to tDCS, and Related Non-Invasive Brain Stimulation Tools. *Clinical Neurophysiology*, **127**, 1031-1048. https://doi.org/10.1016/j.clinph.2015.11.012

[40] Clark, V.P., Coffman, B.A., Trumbo, M.C. and Gasparovic, C. (2011) Transcranial Direct Current Stimulation (tDCS) Produces Localized and Specific Alterations in Neurochemistry: A ^{1}H Magnetic Resonance Spectroscopy Study. *Neuroscience Letters*, **500**, 67-71. https://doi.org/10.1016/j.neulet.2011.05.244

[41] Hone-Blanchet, A., Edden, R.A. and Fecteau, S. (2016) Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites. *Biological Psychiatry*, **80**, 432-438. https://doi.org/10.1016/j.biopsych.2015.11.008

[42] Koolschijn, R.S., *et al*. (2019) The Hippocampus and Neocortical Inhibitory Engrams Protect against Memory Interference. *Neuron*, **101**, 528-541. https://doi.org/10.1016/j.neuron.2018.11.042

[43] Podda, M.V., *et al*. (2016) Anodal Transcranial Direct Current Stimulation Boosts Synaptic Plasticity and Memory in Mice via Epigenetic Regulation of Bdnf Expression. *Scientific Reports*, **6**, Article No. 22180. https://doi.org/10.1038/srep22180

[44] Greer, P.L. and Greenberg, M.E. (2008) From Synapse to Nucleus: Calcium-Dependent Gene Transcription in the Control of Synapse Development and Function. *Neuron*, **59**, 846-860. https://doi.org/10.1016/j.neuron.2008.09.002

[45] Nitsche, M.A., *et al*. (2004) GABAergic Modulation of DC Stimulation-Induced Motor Cortex Excitability Shifts in Humans. *European Journal of Neuroscience*, **19**, 2720-2726. https://doi.org/10.1111/j.0953-816X.2004.03398.x

[46] Stagg, C.J., Bachtiar, V. and Johansen-Berg, H. (2011) The Role of GABA in Human Motor Learning. *Current Biology*, **21**, 480-484. https://doi.org/10.1016/j.cub.2011.01.069

[47] Stafford, J., Brownlow, M. L., Qualley, A. and Jankord, R. (2018) AMPA Receptor Translocation and Phosphorylation Are Induced by Transcranial Direct Current Stimulation in Rats. *Neurobiology of Learning and Memory*, **150**, 36-41. https://doi.org/10.1016/j.nlm.2017.11.002

[48] Fonteneau, C., *et al*. (2018) Frontal Transcranial Direct Current Stimulation Induces Dopamine Release in the Ventral Striatum in Human. *Cerebral Cortex*, **28**, 2636-2646. https://doi.org/10.1093/cercor/bhy093

[49] Nitsche, M.A., *et al*. (2009) Serotonin Affects Transcranial Direct Current-Induced Neuroplasticity in Humans. *Biological Psychiatry*, **66**, 503-508. https://doi.org/10.1016/j.biopsych.2009.03.022

[50] Kuo, M.-F., Grosch, J., Fregni, F., Paulus, W. and Nitsche, M.A. (2007) Focusing Effect of Acetylcholine on Neuroplasticity in the Human Motor Cortex. *Journal of Neuroscience*, **27**, 14442-14447. https://doi.org/10.1523/JNEUROSCI.4104-07.2007

[51] Yu, T.-H., Wu, Y.-J., Chien, M.-E. and Hsu, K.-S. (2019) Transcranial Direct Current Stimulation Induces Hippocampal Metaplasticity Mediated by Brain-Derived Neurotrophic Factor. *Neuropharmacology*, **144**, 358-367. https://doi.org/10.1016/j.neuropharm.2018.11.012

[52] Fritsch, B., Reis, J., Martinowich, K., *et al*. (2010) Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning. *Neuron*, **66**, 198-204. https://doi.org/10.1016/j.neuron.2010.03.035

[53] Decker, A.L. and Duncan, K. (2020) Acetylcholine and the Complex Interdependence of Memory and Attention. *Current Opinion in Behavioral Sciences*, **32**, 21-28. https://doi.org/10.1016/j.cobeha.2020.01.013

[54] Stagg, C.J., *et al*. (2014) Local GABA Concentration Is Related to Network-Level Resting Functional Connectivity. *eLife*, **3**, e01465. https://doi.org/10.7554/eLife.01465

[55] Shafiei, G., *et al*. (2019) Dopamine Signaling Modulates the Stability and Integration of Intrinsic Brain Networks. *Cerebral Cortex*, **29**, 397-409. https://doi.org/10.1093/cercor/bhy264

[56] Shine, J.M., Aburn, M.J., Breakspear, M. and Poldrack, R.A. (2018) The Modulation of Neural Gain Facilitates a Transition Between Functional Segregation and Integration in the Brain. *eLife*, **7**, e31130. https://doi.org/10.7554/eLife.31130

[57] Li, S.-C. and Rieckmann, A. (2014) Neuromodulation and Aging: Implications of Aging Neuronal Gain Control on Cognition. *Current Opinion in Neurobiology*, **29**, 148-158. https://doi.org/10.1016/j.conb.2014.07.009

[58] Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., & Flöel, A. (2013) Anodal Transcranial Direct Current Stimulation Temporarily Reverses Age-Associated Cognitive Decline and Functional Brain Activity Changes. *Journal of Neuroscience*, **33**, 12470-12478. https://doi.org/10.1523/JNEUROSCI.5743-12.2013

[59] Koen, J.D. and Rugg, M.D. (2019) Neural Dedifferentiation in the Aging Brain. *Trends in Cognitive Sciences*, **23**, 547-559. https://doi.org/10.1016/j.tics.2019.04.012

[60] Linnerbauer, M., Wheeler, M.A. and Quintana, F.J. (2020) Astrocyte Crosstalk in CNS Inflammation. *Neuron*, **108**, 608-622. https://doi.org/10.1016/j.neuron.2020.08.012

[61] Steadman, P.E., *et al*. (2020) Disruption of Oligodendrogenesis Impairs Memory Consolidation in Adult Mice. *Neuron*, **105**, 150-164. https://doi.org/10.1016/j.neuron.2019.10.013

[62] Adamsky, A., *et al*. (2018) Astrocytic Activation Generates *de Novo* Neuronal Potentiation and Memory Enhancement. *Cell*, **174**, 59-71. https://doi.org/10.1016/j.cell.2018.05.002

[63] Vainchtein, I.D. and Molofsky, A.V. (2020) Astrocytes and Microglia: In Sickness and in Health. *Trends in Neurosciences*, **43**, 144-154. https://doi.org/10.1016/j.tins.2020.01.003

[64] Du, Z., *et al*. (2021) Knockdown of Astrocytic Grin2a Aggravates β-Amyloid-Induced Memory and Cognitive Deficits through Regulating Nerve Growth Factor. *Aging Cell*, **20**, e13437. https://doi.org/10.1111/acel.13437

[65] Castellani, G. and Schwartz, M. (2020) Immunological Features of Non-neuronal Brain Cells: Implications for Alzheimer's Disease Immunotherapy. *Trends in Immunology*, **41**, 794-804. https://doi.org/10.1016/j.it.2020.07.005

[66] Bartels, T., Schepper, S.D. and Hong, S. (2020) Microglia Modulate Neurodegeneration in Alzheimer's and Parkinson's Diseases. *Science*, **370**, 66-69. https://doi.org/10.1126/science.abb8587

[67] Colonna, M. and Butovsky, O. (2017) Microglia Function in the Central Nervous System during Health and Neurodegeneration. *Annual Review of Immunology*, **35**, 441-468. https://doi.org/10.1146/annurev-immunol-051116-052358

[68] Ruohonen, J. and Karhu, J. (2012) TDCS Possibly Stimulates Glial Cells. *Clinical Neurophysiology*, **123**, 2006-2009. https://doi.org/10.1016/j.clinph.2012.02.082