



Reactivation of Childhood Visual Memory Engrams and Brain Rejuvenation: A New Perspective in Longevity Medicine Based on Neuroplasticity and Epigenetic Regulation

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Abstract

Against the backdrop of global population aging, cognitive decline has become a core bottleneck restricting healthy life expectancy. This article systematically reviews the neurobiological mechanisms by which Childhood Visual Memory Engram Reactivation (CVMER) achieves brain rejuvenation by activating silent memory engrams, promoting neurogenesis, regulating the epigenetic clock, and secreting systemic anti-aging factors. Integrating evidence from the fields of neuroscience, epigenetics, immunology, and clinical medicine, this study proposes the strategic positioning, implementation framework, and future directions of CVMER as an active health intervention in anti-aging longevity medicine. It focuses on elaborating the design principles, indicator system, technical methods, and quality control of a multi-dimensional quantitative evaluation system, supplements and improves the practical details of the quantitative design of the evaluation, and clarifies the quantitative standards, detection frequency, and effect size determination basis of each indicator. This research provides theoretical and practical support for the paradigm shift of anti-aging medicine from "neuroprotection" to "neurorestoration".

Keywords: Childhood Memory, Visual Memory Engram, Neuroplasticity, Epigenetics, Brain Rejuvenation, Longevity Medicine, Active Health, Quantitative Evaluation

Introduction: The Brain as a Rate-Limiting Organ for Longevity

Aging and the Cognitive Crisis

The global aging process is accelerating, and it is estimated that by 2050, the population aged 60 and above will reach 2.1 billion [1]. Cognitive decline—from Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD)—has become the leading cause of disability in the elderly, with over 55 million people with dementia

worldwide and an annual economic burden of 1.3 trillion US dollars [2]. Traditional anti-aging strategies mainly focus on peripheral organs (cardiovascular system, metabolic system, muscles), but increasing evidence indicates that the brain is the rate-limiting organ for longevity [3], and the functional state of the nervous system determines the quality and length of healthy life expectancy.

From Neuroprotection to Neurorestoration

Anti-aging medicine is undergoing a paradigm shift [Table 1]:



Table: 1

Traditional Paradigm	Emerging Paradigm
Passive Defense (Neuroprotection)	Active Repair (Neurorestoration)
Delaying Decline	Functional Reconstruction
Molecular Pathway Targeting	Neural Network Remodeling
Static Intervention	Dynamic Adaptive Intervention

Reactivation of Childhood Visual Memory Engrams (CVMER) is a cutting-edge direction of this transformation. By reactivating memory engrams formed in early developmental stages, it triggers systemic neuroplastic changes to achieve “brain rejuvenation”.

Definition of Core Concepts

- a) Visual Engram:** A sparse population of neurons in the hippocampal-cortical network that encodes visual experiences, with dual physical (synaptic structural changes) and functional (reproduction of activity patterns) properties [4].
- b) Silent Engram:** A memory engram that is functionally silent due to immature neural development or inhibited protein synthesis but retains a structural basis [5].
- c) Infantile Amnesia:** The inability to recall memories before the age of 2-3 years, which is caused by the delayed development of the ability to form engram cell assemblies [6].
- d) Brain Rejuvenation:** Reversing or compensating for age-related neural functional decline through intervention, and restoring a youthful state of cognition, emotion, and neurophysiology [3].

Neurobiological Basis of Childhood Visual Memory Engrams

Molecular Mechanisms of Infantile Amnesia

Early memory circuits are mainly composed of “axonal synapses” containing NMDA receptors with a high GluN2B/GluN2A ratio, and AMPARs (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors) are in a silent state, delaying the process of synaptic “unsilencing”. With the advancement of development:

Table: 2

Characteristics	Neural Basis	Intervention Value
High Emotional Valence	Coordinated encoding of the amygdala and hippocampus (consistent with hippocampal engram reconsolidation in 3.1.1).	Emotional regulation and activation of the reward system (consistent with oxytocin-mediated social emotional regulation in 3.4.1).
Multisensory Integration	Convergence of visual, auditory, olfactory, and tactile senses (consistent with multimodal sensory cue integration in 4.1).	Enhanced effect of multimodal intervention (consistent with hierarchical intervention synergy in 4.1).
S p a t i a l Contextuality	Hippocampal place cells and scene cells (consistent with the hippocampal scene construction target at the enhanced level in 4.1).	VR immersive reconstruction of retrieval cues (consistent with the VR scene reconstruction feature in 4.2).
S o c i a l Embeddedness	Mirror neuron system (consistent with the social cognitive network target at the deepening level in 4.1).	Enhanced social connection through intergenerational interaction (consistent with the VR multi-user intergenerational co-experience in 4.2).

Early stage (Postnatal Day 8, P8) → Adulthood (Postnatal Days 16-20, P16-20)

Decreased GluN2B/GluN2A ratio → Enhanced AMPAR function

Synaptic maturation → Dendritic stability → Sparse neuron activation

Formation of engram cell assemblies [4,6]

This developmental time window prevents early experiences from being encoded into typical engram cell assemblies, forming latent memory engrams—that is, memory engrams with a structural basis but impaired functional retrieval.

Discovery and Characteristics of Silent Memory Engrams

Optogenetic studies (a series of studies by the Tonegawa laboratory) have confirmed [5,7]:

- a. Active Engrams:** Can be activated by natural retrieval cues, with complete synaptic potentiation (Long-Term Potentiation, LTP) and structural plasticity.
- b. Silent Engrams:** Cannot be naturally retrieved, but their synaptic connections are intact; they can be reactivated through targeted interventions (such as optogenetics, specific cue stimulation) and converted into active engrams [5].

The core feature of silent memory engrams is the “functional dissociation” between structure and function: the structural basis (synaptic connections between engram cells) is retained, but the functional connection (neuronal activity synchronization) is temporarily inhibited. This provides a structural basis for the reactivation of childhood visual memory engrams in adulthood.

Unique Characteristics of Childhood Visual Memory Engrams

Compared with adult memory engrams, childhood visual memory engrams have unique neurobiological characteristics, which determine their special value in brain rejuvenation intervention [Table 2]:

Neurobiological Mechanisms of CVMER-Mediated Brain Rejuvenation

CVMER achieves brain rejuvenation through a “multi-level, multi-pathway” regulatory network, involving four core links: engram reactivation, neurogenesis promotion, epigenetic clock regulation, and systemic anti-aging factor secretion. These links interact synergistically to form a complete regulatory loop.

Engram Reactivation and Neural Network Remodeling

Reconsolidation of Memory Engrams: Memory engrams are not static; they undergo continuous reconsolidation during retrieval. When childhood visual memory engrams are reactivated, the following processes occur [8,9]:

- a. Retrieval cue stimulation (such as childhood visual images) activates the hippocampal-cortical network, triggering the depolarization of engram cells.
- b. Depolarization leads to the insertion of AMPARs into the synaptic membrane, converting silent synapses into active synapses (synaptic unsilencing).
- c. Activated engram cells secrete Brain-Derived Neurotrophic Factor (BDNF), promoting the proliferation of dendritic spines and the formation of new synaptic connections.
- d. The reconsolidated engram cell assemblies have stronger functional connectivity, improving the efficiency of memory retrieval and neural information processing.

This process not only restores the function of silent memory engrams but also remodels the hippocampal-cortical neural network, reversing age-related neural network degradation.

Coordination of Neural Circuits: CVMER mainly regulates three core neural circuits related to brain aging:

- a. **Hippocampal-Prefrontal Cortex Circuit:** It is the core circuit for memory and executive function; age-related decline in its functional connectivity is the main cause of memory loss and executive function impairment [10]. CVMER can significantly enhance the functional connectivity of this circuit, improve the synchronization of neuronal activity, and restore the regulatory ability of the prefrontal cortex on hippocampal memory function.
- b. **Default Mode Network (DMN):** It is closely related to self-awareness, memory retrieval, and emotional regulation; its abnormal activation is associated with cognitive decline and depression in the elderly [11]. CVMER can regulate the activity of the DMN, reduce its excessive activation, and restore its balance with the task-positive network.
- c. **Amygdala-Hippocampus Circuit:** It is involved in emotional memory encoding and retrieval; age-related weakening of its function leads to decreased emotional regulation ability [12]. CVMER, through the high emotional valence of childhood memories, activates this circuit, promotes the coordinated activity of the amygdala and hippocampus, and

improves emotional stability.

Promotion of Hippocampal Neurogenesis

Hippocampal neurogenesis (the continuous generation of new neurons in the hippocampal dentate gyrus in adulthood) is an important basis for neuroplasticity. It decreases significantly with age, and the reduction in hippocampal neurogenesis is closely related to memory decline and cognitive impairment [13]. CVMER promotes hippocampal neurogenesis through two pathways:

Activation of Neural Stem Cells (NSCs): Childhood visual memory engram reactivation can activate quiescent neural stem cells in the hippocampal dentate gyrus, promoting their proliferation and differentiation into mature neurons [14]. The specific mechanism is as follows: activated engram cells secrete BDNF and Vascular Endothelial Growth Factor (VEGF), which bind to their receptors on neural stem cells, activate the PI3K-Akt and MAPK signaling pathways, and promote the proliferation and differentiation of neural stem cells.

Optimization of the Neurogenic Microenvironment: The neurogenic microenvironment (including glial cells, blood vessels, and extracellular matrix) plays a key role in regulating hippocampal neurogenesis. Age-related chronic inflammation and oxidative stress damage the neurogenic microenvironment, inhibiting neurogenesis [15]. CVMER can inhibit the activation of microglia (reduce the secretion of pro-inflammatory factors such as TNF- α and IL-6), increase the number of astrocytes that secrete neurotrophic factors, and reduce oxidative stress (increase the activity of superoxide dismutase, SOD), thereby optimizing the neurogenic microenvironment and providing a favorable condition for the survival and integration of new neurons.

Epigenetic Clock Regulation

The epigenetic clock (a set of epigenetic markers that can accurately predict age) is an important indicator of biological aging. Age-related changes in epigenetic modifications (such as DNA methylation, histone modification, and non-coding RNA regulation) lead to the silencing of anti-aging genes and the activation of pro-aging genes, accelerating brain aging [16]. CVMER regulates the epigenetic clock through multiple epigenetic modifications, reversing the epigenetic aging process of the brain.

DNA Methylation Regulation: CVMER can regulate the activity of DNA Methyltransferases (DNMTs) and Demethylases (TETs), changing the DNA methylation level of key genes related to brain aging [17]. For example, CVMER can reduce the DNA methylation level of the BDNF gene promoter, promote BDNF transcription and expression; at the same time, it can increase the DNA methylation level of the pro-inflammatory factor TNF- α gene promoter, inhibit its expression, thereby reducing neuroinflammation.

Histone Modification Regulation: Histone acetylation and methylation are important forms of histone modification, which regulate gene expression by changing the structure of chromatin. CVMER can activate histone acetyltransferases (such as CBP/p300) and Inhibit Histone Deacetylases (HDACs), increasing the acetylation

level of histones in the promoter region of neuroplasticity-related genes (such as BDNF, CREB), promoting gene transcription [18]. In addition, CVMER can also regulate histone methylation (such as H3K4me3, H3K27me3), adjust the expression of neurogenesis-related genes, and promote hippocampal neurogenesis.

Non-Coding RNA Regulation: Non-coding RNAs (such as microRNAs, miRNAs; long non-coding RNAs, lncRNAs) play an important regulatory role in brain aging and neuroplasticity. CVMER can regulate the expression level of miRNAs related to brain aging. For example, CVMER can down-regulate the expression of miR-124 (which inhibits neural stem cell differentiation) and up-regulate the expression of miR-132 (which promotes synaptic plasticity), thereby promoting neurogenesis and synaptic remodeling.

Secretion of Systemic Anti-Aging Factors

The brain is not an isolated organ; it interacts with peripheral organs through the neuroendocrine-immune network. CVMER can trigger the brain to secrete a variety of systemic anti-aging factors, which act on peripheral organs, forming a “brain-peripheral” anti-aging regulatory loop, thereby achieving overall aging delay while realizing brain rejuvenation.

Regulation of the Neuroendocrine System: CVMER activates the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Hypothalamic-Pituitary-Gonadal (HPG) axis, promoting the secretion of anti-aging hormones. For example, CVMER can promote the hypothalamus to secrete Growth Hormone-Releasing Hormone (GHRH), promoting the pituitary gland to secrete Growth Hormone

(GH); GH can promote the proliferation of cells in peripheral organs (such as muscles, bones) and delay their aging. In addition, CVMER can also promote the secretion of oxytocin, which not only improves social connection and emotional regulation but also has anti-inflammatory and anti-oxidative stress effects, protecting the brain and peripheral organs from aging damage.

Regulation of the Immune System: Chronic inflammation (inflammaging) is a core mechanism of aging. CVMER can regulate the function of the immune system, inhibit chronic inflammation, and promote the secretion of anti-inflammatory factors. Specifically, CVMER can inhibit the activation of microglia in the brain and macrophages in peripheral organs, reduce the secretion of pro-inflammatory factors (TNF- α , IL-6, IL-1 β), and increase the secretion of anti-inflammatory factors (IL-10, TGF- β). At the same time, CVMER can enhance the function of regulatory T cells (Tregs), which further inhibits the excessive immune response and reduces chronic inflammation.

Secretion of Myokines and Cytokines: CVMER can indirectly promote the secretion of myokines (muscle-derived cytokines) and cytokines by regulating the brain-muscle communication pathway. For example, CVMER activates the motor cortex, promotes muscle contraction, and triggers muscle cells to secrete myokines such as irisin and BDNF; these myokines enter the brain through the blood-brain barrier, further promoting neurogenesis and synaptic plasticity. In addition, CVMER can also promote the secretion of cytokines such as VEGF and IGF-1, which have neuroprotective and anti-aging effects [Table 3].

Table: 3

Pathways	Molecular Mechanisms	Functional Consequences
BDNF Upregulation	TrkB receptor activation, CREB phosphorylation (consistent with CREB regulation by histone acetylation in 3.3.1).	Neuronal survival, differentiation, synaptic plasticity (consistent with the LTP protein synthesis mechanism in 3.1.1).
IGF-1 Release	Peripheral-central signaling, blood-brain barrier permeability (consistent with peripheral-central communication of systemic factors in 3.4.1).	Neural stem cell proliferation, angiogenesis (consistent with the angiogenesis function of VEGF in 3.4.1).
VEGF Secretion	Maintenance of neurovascular niche function (consistent with the optimization of the hippocampal neurogenic microenvironment in 3.2.1).	Integration of newborn neurons, cognitive flexibility (consistent with the evaluation of working memory cognitive flexibility in 5.2.1).
Inflammation Inhibition	Microglial phenotype switching (M1→M2) (consistent with the anti-inflammatory mechanism of immune regulation in 3.4.2).	Optimization of the neurogenic microenvironment (consistent with the requirements of the hippocampal neurogenesis microenvironment in 3.2.1).

Implementation Framework of CVMER in Longevity Medicine

Based on the neurobiological mechanisms of CVMER-mediated brain rejuvenation, this study constructs a “targeted, hierarchical, and personalized” CVMER intervention implementation framework, including three core links: intervention target positioning, hierarchical intervention design, and personalized adjustment strategy.

Intervention Target Positioning

The core target of CVMER intervention is silent childhood visual

memory engrams. Before intervention, it is necessary to accurately locate the distribution and functional state of silent memory engrams through neuroimaging (fMRI, MEG) and molecular detection (BDNF, miRNA expression level), clarify the key neural circuits and molecular pathways that need to be regulated, and lay a foundation for targeted intervention.

The positioning indicators mainly include:

a. Neuroimaging Indicators: Functional connectivity of the hippocampal-prefrontal cortex circuit, activity level of the default mode network, and regional cerebral blood flow (rCBF) in the hippocampus.

b. Molecular Indicators: Expression levels of BDNF, VEGF, miR-132, and miR-124 in the hippocampus and peripheral blood.

c. Cognitive Indicators: Memory function (episodic memory, working memory), executive function, and emotional regulation ability.

Hierarchical Intervention Design

According to the functional state of silent memory engrams and the level of cognitive decline, CVMER intervention is divided into five levels, with gradual deepening and progressive improvement, to achieve precise intervention [Table 4]:

Table: 4

Levels	Technical Methods	Neural Targets	Expected Effects
Basic Level	High-definition restoration and dynamization of childhood photos (consistent with the object encoding of visual memory in 2.3).	Ventral visual stream (V1-IT) (consistent with the MEG visual cortex V1-V4 target in 5.2.2).	Activation of object recognition memory (consistent with the evaluation of episodic memory object recognition in 5.2.1).
Enhanced Level	VR immersive reconstruction of childhood environments (consistent with the VR time travel illusion feature in 4.2).	Hippocampal scene construction system (consistent with the function of hippocampal place cells in 2.3).	Context-dependent retrieval (consistent with the context dependence of engram reconsolidation in 3.1.1).
Integration Level	Sensorimotor reproduction of childhood games (consistent with the multisensory integration feature in 2.3).	Sensorimotor cortex, cerebellum (consistent with the coordination between neural network modules in 3.1.2).	Procedural memory restoration (consistent with the evaluation of working memory procedural memory in 5.2.1).
Deepening Level	AI voice/avatar interaction with significant others (consistent with the VR multi-user sharing feature in 4.2).	Social cognitive network (TPJ, mPFC) (consistent with the social function of the mirror neuron system in 2.3).	Attachment memory repair (consistent with the social embeddedness of visual memory in 2.3).
Transformation Level	Narrative integration writing of childhood-adulthood (consistent with the self-processing function of the default mode network in 3.1.2).	Default mode network (consistent with the regulation of DMN activity in 3.1.2).	Self-continuity reconstruction (consistent with the overall recovery target of cognitive function in 5.2.1).

Personalized Adjustment Strategy

Individual differences (age, gender, cognitive level, genetic background, childhood experience) have an important impact on the effect of CVMER intervention. Therefore, it is necessary to formulate a personalized intervention plan and dynamically adjust it according to the intervention effect.

Key adjustment factors include:

a. Age: For young and middle-aged people (30-50 years old), focus on the basic level and enhanced level intervention to maintain neuroplasticity; for the elderly (over 60 years old), focus on the integration level and deepening level intervention to restore cognitive function.

b. Cognitive Level: For people with normal cognitive function, focus on preventive intervention to delay cognitive decline; for people with mild cognitive impairment, focus on targeted intervention to restore memory and executive function.

c. Childhood Experience: For people with positive

childhood experiences, use positive visual cues to enhance intervention effects; for people with negative childhood experiences, combine emotional regulation to repair attachment memory and avoid negative emotional stimulation.

d. Genetic Background: For people with genetic susceptibility to cognitive decline (such as APOE ε4 carriers), increase the intervention frequency and strengthen the regulation of neuroprotective pathways (such as BDNF and VEGF).

Multi-Dimensional Quantitative Evaluation System for CVMER Intervention Effect

Design Principles of the Evaluation System

The evaluation of CVMER intervention effects follows the SMART-R principle. Combining the scientificity and operability of quantitative evaluation, the quantitative implementation details of each principle are supplemented to ensure that the evaluation indicators are operable, the data are traceable, and the results are comparable [Table 5]:

Table: 5

Principle	Connotation	Implementation Points	Quantitative Implementation Details
S (Specific) Specificity	Targeting specific cognitive domains and neural mechanisms	Distinguishing episodic memory, working memory, and executive function	1-2 core quantitative indicators are defined for each cognitive domain to avoid indicator overlap; neuro-mechanism evaluation corresponds to clear molecular targets (e.g., BDNF) or neural circuits (e.g., hippocampal-prefrontal connectivity).

M (Measurable) Quantifiability	Combination of objective indicators and subjective reports	Standardized tests + biomarkers + neuroimaging	Objective indicators have clear value ranges and detection accuracy (e.g., BDNF detection accuracy $\leq 5\text{pg/mL}$); subjective reports adopt standardized scale scoring with clear scoring rules and classification standards.
A (Accessible) Accessibility	Technically feasible and cost-controllable	Hierarchical evaluation, prioritizing core indicators	The detection cost of core indicators (e.g., Mini-Cog test, serum BDNF) is ≤ 500 yuan per person, and the detection time is ≤ 30 minutes; complex indicators (e.g., fMRI) are detected once every 6 weeks to control the overall evaluation cost.
R (Repeatable) Repeatability	Longitudinal tracking and dynamic monitoring	Four time points: baseline - during intervention - post-intervention - follow-up	The same detection equipment and personnel are used for the same indicator, with fixed detection intervals (e.g., core cognitive indicators detected once every 2 weeks), and the coefficient of variation of detection results is $\leq 10\%$.
T (Time-bound) Timeliness	Capturing acute and chronic effects	Immediate effects (hours), short-term effects (weeks), long-term effects (months-years)	Immediate effects are detected within 1 hour after intervention, short-term effects are detected every 2 weeks, and long-term effects are detected every 3 months, with clear criteria for determining indicator changes at each time stage.
R (Responsive) Responsiveness	Sensitive to intervention and able to detect changes	Selecting moderately difficult tasks to avoid floor/ceiling effects	Preliminary experiments verify indicator responsiveness, ensuring that the indicator change after intervention is \geq the Minimum Clinically Important Difference (MCID), and the change rate $\geq 10\%$ can be stably detected.

Four-Dimensional Evaluation Index System

The quantitative standards, detection method details, and outlier handling schemes of indicators in each dimension are improved, the correlation between indicators is clarified, and an operable and verifiable quantitative evaluation network is constructed to ensure that the evaluation results can accurately reflect the neurobiological effects and clinical value of CVMER

intervention.

Cognitive Function Dimension: Focusing on the core cognitive domains related to CVMER intervention, the operating specifications of each evaluation tool, the basis for determining quantitative standards, and the outlier handling methods are supplemented to ensure the objectivity and consistency of cognitive function evaluation [Table 6]:

Table: 6

Cognitive Domain	Evaluation Tools	Key Indicators	Quantitative Standards	Operating Specifications and Outlier Handling
Episodic Memory	AVLT, WMS-IV Logical Memory	Immediate recall, delayed recall, recognition	A Z-score change ≥ 0.5 is considered effective; an increase of ≥ 1.5 points in delayed recall score (MCID) is considered clinically effective.	AVLT uses 15 disyllabic words, with 5 learning sessions and 3 recall sessions at fixed intervals; outliers (scores deviating from the mean $\pm 2SD$) need to be reviewed in combination with clinical symptoms to rule out detection errors.
Working Memory	CANTAB SWM, N-back	Span, accuracy, reaction time	Accuracy increased by $\geq 10\%$, reaction time shortened by $\geq 15\%$; N-back (2-back) accuracy $\geq 70\%$ is considered normal.	N-back task stimuli are presented for 500ms with an interval of 1000ms; abnormally prolonged reaction time (\geq mean $+2SD$) needs to rule out interfering factors such as inattention.
Executive Function	TMT-B, Stroop, WCST	Completion time, interference effect, number of categories	TMT-B time shortened by $\geq 20\%$; the number of correct WCST categories ≥ 4 is considered normal.	TMT-B paper specifications are uniform, and timing is accurate to the second; the Stroop task uses two paradigms (color-word consistent and inconsistent), and the interference effect is quantified as the reaction time difference between the two paradigms.

Processing Speed	DSST, TMT-A	Completion quantity/time	Speed increased by $\geq 15\%$; completing ≥ 30 items per minute in DSST is considered normal.	DSST uses a standard digital symbol correspondence table, with a fixed detection time of 90 seconds; abnormally low completion quantity needs to rule out interfering factors such as visual impairment.
Visuospatial Function	BVMT-R, Rey-Osterrieth Complex Figure Test	Copy, recall, structure score	Recall score increased by $\geq 20\%$; a structure score ≥ 8 points (10-point scale) is considered normal.	The copying time of the Rey-Osterrieth Complex Figure is ≤ 10 minutes, with a recall interval of 30 minutes; scoring adopts a standardized scoring scale, conducted by 2 evaluators in a double-blind manner, with $ICC \geq 0.85$.
Attention Network	ANT, CPT	Alertness, orientation, executive control	Network efficiency index increased by ≥ 0.3 ; CPT hit rate $\geq 90\%$ is considered normal.	The ANT task includes 3 subtasks: alertness, orientation, and executive control, with 20 trials for each subtask; the network efficiency index is calculated using a standardized formula, excluding trials with reaction errors.

Neurophysiological Dimension: The technical parameters of each detection method, the quantitative basis of core parameters, and the detection quality control standards are supplemented, the correlation analysis method between neurophysiological indicators and cognitive function indicators is clarified, and precise quantitative evaluation at the neurophysiological level is realized [Table 7]:

Table: 7

Indicator Category	Detection Method	Core Parameters	Normal Reference/Target Change	Technical Parameters and Quality Control
Structural Imaging	3T MRI (T1, T2, FLAIR)	Hippocampal volume, cortical thickness, white matter hyperintensities	Annual hippocampal volume change $< 1.5\%$; no significant decrease in cortical thickness; white matter hyperintensity score < 2 points (Fazekas scale)	T1-weighted imaging parameters: $TR=2500ms$, $TE=2.98ms$, slice thickness=1mm; hippocampal volume is automatically segmented using FreeSurfer software with a segmentation accuracy $\geq 90\%$; phantom calibration is performed before each batch of detection.
Functional Imaging	fMRI (resting-state + task-state)	Hippocampal-prefrontal functional connectivity, DMN activity	Functional connectivity strength increased by $\geq 15\%$; DMN activity fluctuates within the normal reference range	Resting-state fMRI scanning time=8 minutes, $TR=2000ms$, $TE=30ms$; task-state adopts a memory retrieval paradigm with a stimulus presentation time of 3000ms; data preprocessing is performed using SPM12 software, with head motion correction $\leq 2mm/2^\circ$.
White Matter Integrity	DTI (64 directions)	FA, MD, RD, AD values	FA value is stable or increased; no significant increase in MD, RD, AD values (change rate $< 5\%$)	DTI scanning parameters: $TR=8000ms$, $TE=80ms$, $b\text{-value}=1000s/mm^2$; fiber tract tracing is performed using FSL software, and the FA value measurement area is the hippocampal-prefrontal fiber tract.
Cerebral Blood Perfusion	ASL-MRI	CBF in hippocampus and prefrontal cortex	CBF increased by $\geq 10\%$; hippocampal CBF $\geq 40mL/(100g\cdot min)$	ASL-MRI adopts the PASL sequence, $TR=4000ms$, $TE=10ms$; CBF is calculated using a standardized formula, excluding interfering factors such as vascular malformations.
Neuroelectrophysiology	64-channel EEG/ERP	$\theta\text{-}\gamma$ coupling, P300 amplitude/latency	P300 amplitude increased by $\geq 20\%$, latency shortened by $\geq 10\%$; $\theta\text{-}\gamma$ coupling coefficient increased by ≥ 0.1	EEG sampling rate=250Hz, electrode impedance $\leq 5k\Omega$; ERP adopts the Oddball paradigm with a stimulus interval of 1000ms; data preprocessing excludes ocular and myoelectric interference, with valid trials $\geq 80\%$.

Autonomic Nervous System	HRV analysis (24h Holter)	SDNN, RMSSD, HF power	HRV index increased by $\geq 15\%$; SDNN ≥ 100 ms, RMSSD ≥ 20 ms	Holter recording time=24 hours, sampling rate=128Hz; HRV analysis adopts a combination of time-domain and frequency-domain methods, excluding interfering factors such as arrhythmia and exercise, with valid recording time ≥ 22 hours.
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Biomarker Dimension: The detection time, sample processing specifications, detection accuracy, and result determination standards of each biomarker are clarified, the synergistic analysis method between biomarkers is supplemented, and a biomarker quantitative evaluation panel is constructed to realize quantitative evaluation of intervention effects at the molecular level [Table 8]:

Table: 8

Biomarker Category	Specific Indicators	Detection Method	Target Change	Sample Processing and Detection Specifications
Neurotrophic Factors	BDNF (serum/plasma)	ELISA	Increased by $\geq 20\%$; serum BDNF ≥ 10 ng/mL is considered normal	5mL of fasting venous blood is collected, centrifuged at 3000r/min for 10min at 4°C, and the serum is separated and stored at -80°C; the ELISA detection kit has a sensitivity ≤ 1 pg/mL, inter-batch variation $\leq 8\%$, and intra-batch variation $\leq 5\%$.
	IGF-1	Chemiluminescence	Maintain a youthful level (reference range is formulated according to age and gender)	Sample collection is the same as BDNF; the detection accuracy of chemiluminescence is ≤ 0.1 ng/mL, and standard curve verification is performed before detection with $R^2 \geq 0.99$.
	VEGF	ELISA	Moderately increased (promoting vascular health); serum VEGF ≥ 50 pg/mL	Sample storage time ≤ 6 months; ELISA detection adopts the double-antibody sandwich method to avoid interference from hemolyzed samples.
Inflammatory Biomarkers	IL-6, TNF- α , hs-CRP	High-sensitivity ELISA	Decreased by $\geq 25\%$; hs-CRP < 3 mg/L, IL-6 < 7 pg/mL, TNF- α < 10 pg/mL	Centrifugation is completed within 2 hours after blood collection; the high-sensitivity ELISA has a sensitivity ≤ 0.1 pg/mL, and the inter-batch consistency ICC ≥ 0.9 .
	IL-10, TGF- β	ELISA	Anti-inflammatory factors increased by $\geq 15\%$; IL-10 ≥ 5 pg/mL	Samples should avoid repeated freezing and thawing (≤ 3 times); samples are diluted before detection to ensure that the detection value is within the range of the standard curve.
Oxidative Stress	8-OHdG, MDA, SOD	Colorimetry/ELISA	Oxidative damage decreased by $\geq 20\%$, antioxidant capacity increased by $\geq 15\%$; SOD ≥ 120 U/mL	8-OHdG detection uses urine samples (5mL of morning urine), and MDA and SOD use serum samples; the detection wavelength of colorimetry is fixed, and blank control calibration is performed.
Metabolic Biomarkers	Insulin, HOMA-IR	Biochemical analysis	Insulin sensitivity improved; HOMA-IR < 2.5	Blood is collected after 12 hours of fasting; insulin detection adopts radioimmunoassay with an accuracy ≤ 1 μ IU/mL; HOMA-IR=(fasting insulin \times fasting blood glucose)/22.5.
	Adiponectin, Leptin	ELISA	Metabolic balance optimized; adiponectin ≥ 5 μ g/mL, leptin within the age and gender reference range	Sample collection is the same as BDNF; the incubation time between the ELISA detection kit and the sample is fixed at 60 minutes to avoid interference from temperature fluctuations.
Epigenetics	DNA methylation age (Horvath clock)	Infinium methylation chip	The rate of biological age increase slows down or reverses (annual increase rate < 1 year)	Peripheral blood mononuclear cells (PBMC) are isolated after blood collection, and genomic DNA is extracted with a purity OD260/OD280=1.8-2.0; chip detection adopts the Illumina Infinium MethylationEPIC chip with a probe detection rate $\geq 95\%$.

Psychosocial Dimension: The scoring rules of each evaluation tool, the basis for determining the threshold of clinical significance, and the quality control methods of subjective evaluation are supplemented to realize quantitative evaluation at the psychosocial level, taking into account both subjective experience and objective performance [Table 9]:

Table: 9

Evaluation Domain	Tools	Dimensions/Indicators	Threshold of Clinical Significance	Scoring Rules and Quality Control
Nostalgic Function	Southampton Nostalgia Scale (SNS)	Frequency, affect, sociality, personal-history	Total score increased by $\geq 10\%$; total score ≥ 60 points (100-point scale) is considered good	The scale consists of 20 items, using a 5-point scoring system (1=completely inconsistent, 5=completely consistent); total score=sum of scores of each item; during evaluation, ensure that the subjects understand the meaning of the items to avoid ambiguity, and the filling time ≤ 10 minutes.
Self-Continuity	Self-Continuity Index (SCI)	Past-present-future connection	Increased by ≥ 0.5 standard deviations; SCI ≥ 3 points (5-point scale) is considered normal	It adopts a combination of visual analog scoring and questionnaire scoring, with 10 items, each scored 1-5 points; evaluators need to be trained, and a unified standard is adopted for the determination of ambiguous answers.
Meaning in Life	Meaning in Life Questionnaire (MLQ)	Presence of meaning, search for meaning	Presence of meaning increased by $\geq 15\%$; presence of meaning dimension score ≥ 20 points (30-point scale)	The scale consists of 10 items, using a 7-point scoring system (1=completely inconsistent, 7=completely consistent); scoring is performed separately for the presence of meaning and search for meaning dimensions to avoid dimension confusion; check completeness after filling, and missing items ≤ 1 can be filled by mean imputation.
Emotional State	GDS-15, HADS, PANAS	Depression, anxiety, positive/negative affect	GDS decreased by $\geq 30\%$; GDS < 5 points is considered normal, and HADS anxiety/depression dimension < 8 points is considered normal	GDS-15 consists of 15 items, Yes=1 point, No=0 point; HADS consists of 14 items, using a 4-point scoring system; PANAS consists of 20 items, using a 5-point scoring system; avoid suggestive questions during evaluation to ensure that subjects express their emotions truthfully.
Quality of Life	WHO-QOL-OLD, SF-36	Physical, psychological, social, environmental	Total score increased by $\geq 10\%$; WHO-QOL-OLD total score ≥ 60 points (100-point scale) is considered good	WHO-QOL-OLD consists of 24 items, using a 5-point scoring system; SF-36 consists of 36 items, and each dimension score is standardized to 0-100 points; total score=mean of standardized scores of each dimension; for elderly subjects, oral questioning can be used for filling during evaluation.
Social Connection	Social Network Index (SNI), UCLA Loneliness Scale	Network size, loneliness	Loneliness decreased by $\geq 20\%$; UCLA Loneliness Scale < 20 points is considered normal, and SNI ≥ 5 points is considered good	The UCLA Loneliness Scale consists of 20 items, using a 4-point scoring system; SNI is scored from 3 dimensions: social network size, frequency, and satisfaction; check logical consistency after filling to avoid contradictory answers.
Cognitive Reserve	Cognitive Reserve Index Questionnaire (CRIq)	Education, occupation, leisure	Maintained or increased; CRIq ≥ 25 points (40-point scale) is considered normal	The questionnaire consists of 16 items, using hierarchical scoring; scoring is performed separately for education, occupation, and leisure dimensions with consistent weights for each dimension; during evaluation, accurately record the subject's education years and occupation type to ensure accurate scoring.

Design of Evaluation Time Points and Procedures

The time node design of evaluation time points is optimized, the operation procedures, sample collection and detection sequence of each time point evaluation are supplemented, the entry and review

specifications of evaluation data are clarified, and a standardized longitudinal quantitative evaluation procedure is constructed to ensure the consistency and continuity of evaluation at each time point:

Longitudinal Evaluation Framework: [Table 10]

Table: 10

Time Point	Time Node	Core Evaluation Content	Evaluation Purpose	Operating Specifications and Data Management
Baseline Evaluation (T0)	Within 1 week before the start of intervention	Comprehensive detection of four-dimensional indicators; collection of demographic data, medical history, and medication history	Establish individual baseline level, screen eligible subjects, and exclude contraindications	Detection is performed in the order of "cognition → psychosocial → biological samples → neuroimaging"; data are double-entry by two persons, archived after verification, and marked with baseline identification.
Immediate Effect Evaluation (T1)	Within 1 hour after the first intervention	Cognition (immediate recall of episodic memory), neuroelectrophysiology (ERP), autonomic nervous system (HRV), subjective emotion (PANAS)	Verify the acute effect of a single intervention and optimize intervention parameters	ERP and HRV are collected immediately to avoid state fluctuations after subject's rest; subjective scales are filled on the spot, and immediate feelings after intervention are recorded.
Short-Term Effect Evaluation (T2)	2 weeks after intervention (3 times a week, 6 times in total)	Cognition (core domains), psychosocial (emotion, nostalgia), biomarkers (BDNF, inflammatory factors)	Monitor short-term intervention effects and judge intervention tolerance	Fasting biological samples are collected, consistent with the baseline sampling time; cognitive tests adopt the same operating specifications as baseline to reduce errors.
Mid-Term Effect Evaluation (T3)	6 weeks after intervention (18 standardized interventions completed)	Comprehensive detection of four-dimensional indicators; evaluation of intervention adherence	Comprehensively evaluate mid-term intervention effects and adjust intervention plans if necessary	The same equipment and parameters as baseline are used for neuroimaging; adherence is calculated (actual intervention times/planned intervention times $\geq 80\%$ is considered qualified).
Post-Intervention Evaluation (T4)	Within 1 week after the end of intervention (12 weeks in total, 36 interventions)	Comprehensive detection of four-dimensional indicators; investigation of intervention satisfaction	Summarize the total intervention effect and verify intervention effectiveness	Compare with baseline and mid-term data to calculate the indicator change rate; satisfaction survey adopts a 5-point scale, and subjects' feedback and suggestions are recorded simultaneously.
Follow-Up Evaluation (T5-T6)	3 months (T5) and 6 months (T6) after intervention	Cognition (core domains), biomarkers (key indicators), psychosocial (core dimensions)	Evaluate the persistence of intervention effects and monitor long-term safety	Remind subjects 1 week in advance to ensure follow-up adherence; data are compared with previous data to analyze the attenuation of effects and record adverse events.

Supplementary Note: Evaluation at each time point must strictly follow the "Standard Operating Procedure (SOP)", clarify the time nodes for sample collection, transportation, and detection (e.g., biological samples are centrifuged within 2 hours after collection and stored at -80°C), neuroimaging data must be uniformly preprocessed, and cognitive and psychosocial evaluations must be completed by professionally trained evaluators to ensure consistency between different time points and different evaluators ($\text{ICC} \geq 0.85$).

Quality Control and Data Statistical Methods

To ensure the authenticity, reliability, and scientificity of evaluation data, the specific measures of the quality control system and data statistical analysis methods are supplemented and improved, the statistical test standards and the basis for determining effect size are clarified, and the repeatability and verifiability of quantitative evaluation results are ensured to provide support for the accurate determination of intervention effects:

Whole-Process Quality Control Measures

i. Personnel Quality Control: All evaluators must complete special training on cognitive evaluation, biological sample processing, neuroimaging operation, etc., and can take up

their posts only after passing the assessment; regular re-training and assessment are carried out to unify evaluation standards and reduce human errors; an evaluator coding system is established to facilitate responsibility tracing.

ii. Equipment and Reagent Quality Control: Detection equipment (MRI, EEG, ELISA detector, etc.) is calibrated regularly (routine calibration once a month, comprehensive calibration once every 6 months), and calibration reports are recorded; reagents of the same brand and batch are used, and the storage conditions and service life specified in the reagent instructions are strictly followed; blank controls and positive controls are set for each detection to verify reagent effectiveness; biological sample collection tools are for one-time use to avoid cross-contamination.

iii. Data Quality Control: A double-entry mode by two persons is adopted for data entry; after entry, logical verification and range verification are performed (e.g., BDNF detection values exceeding the normal range need to be rechecked); invalid data are deleted (e.g., scales with missing items $>10\%$, fMRI data with head motion exceeding $2\text{mm}/2^{\circ}$); a data traceability mechanism is established, and each data point corresponds to a complete detection record and evaluation log to ensure data traceability; data are stored in an encrypted manner to protect subjects' privacy.

iv. Intervention Adherence Quality Control: An intervention log is established to record the time, duration, and subject status of each intervention; subjects are reminded to participate in the intervention on time every week; targeted communication is conducted with subjects with low adherence (<80%) to analyze the reasons and adjust the intervention plan; adherence data are included in the final statistical analysis as an important basis for adjusting effect size.

v. Quality Inspection: A quality control team is established to conduct random inspections of evaluation data and operation procedures every 2 weeks (sampling ratio $\geq 10\%$), and problems

are rectified in a timely manner; a comprehensive quality review is conducted after the end of the intervention to summarize quality control points and improvement directions and form a quality control report.

Data Statistical Analysis Methods: Combined with the type of evaluation data (measurement data, count data) and the characteristics of longitudinal tracking, appropriate statistical methods are adopted to clarify the statistical test level and the basis for determining effect size, ensuring the scientificity and rationality of statistical analysis [Table 11]:

Table: 11

Data Type	Statistical Methods	Application Scenarios	Test Level and Effect Size Determination
Measurement data (normal distribution)	Paired t-test, repeated measures Analysis of Variance (ANOVA), Pearson correlation analysis	Comparison of indicators of the same subject at different time points, correlation analysis between indicators, comparison of inter-group effects	Test level $\alpha=0.05$; effect size Cohen's $d \geq 0.5$ is medium effect, ≥ 0.8 is large effect.
Measurement data (non-normal distribution)	Wilcoxon signed-rank test, Kruskal-Wallis H test, Spearman correlation analysis	Time point comparison of non-normally distributed biomarkers (e.g., inflammatory factors) and subjective scale scores	Test level $\alpha=0.05$; effect size $r \geq 0.3$ is medium correlation, ≥ 0.5 is strong correlation.
Count data	χ^2 test, Fisher's exact test	Comparison of subject group composition, qualification of intervention adherence, incidence of adverse events	Test level $\alpha=0.05$; relative risk (RR) ≥ 2 or ≤ 0.5 is a significant association.
Multivariate analysis	Multiple linear regression, Logistic regression, mixed-effects model	Analyze the impact of confounding factors such as age, gender, and education years on intervention effects and correct confounding effects	$P < 0.05$ is considered statistically significant; $R^2 \geq 0.2$ indicates good model fitting.

Supplementary Note: Statistical analysis is completed using SPSS 26.0 and R 4.2.0 software; all statistical results need to report test statistics, P values, effect sizes, and 95% confidence intervals; for longitudinal tracking data, a mixed-effects model is used to correct intra-individual variation to ensure the reliability of statistical results; if there are missing data (missing rate <10%), multiple imputation is used for imputation; if the missing rate >10%, the sample is excluded.

Discussion and Outlook

Core Findings and Theoretical Innovations

This article systematically sorts out the neurobiological mechanisms by which Childhood Visual Memory Engram Reactivation (CVMER) induces brain rejuvenation remodeling, clarifying that it achieves a paradigm shift from "neuroprotection" to "neurorestoration" by activating silent engrams, enhancing synaptic plasticity, promoting adult neurogenesis, regulating the epigenetic clock, and secreting systemic anti-aging factors, providing a new active health intervention target for longevity medicine. Compared with traditional anti-aging strategies focusing on peripheral organs or a single molecular pathway, CVMER has the advantage of multi-dimensional and multi-system integration. Its core innovation lies in: taking childhood visual memory, a memory carrier with high emotional valence and multi-sensory integration, as the entry point,

and utilizing the lifelong retention of neuroplasticity to realize active remodeling of brain function rather than passive delay of decline; at the same time, a four-dimensional quantitative evaluation system covering cognition, neurophysiology, biomarkers, and psychosocial aspects is constructed, supplementing highly operable evaluation details, quality control measures, and statistical methods, solving the pain points of traditional intervention effect evaluation such as lack of standardization and poor operability, and providing theoretical and practical support for the clinical transformation of CVMER.

In addition, this article proposes that "silent engram desilencing" may be a key window period for early intervention in Alzheimer's disease. The high social embeddedness and multi-sensory characteristics of childhood visual memory can be accurately awakened through VR technology, intergenerational interaction, etc., providing a new idea for early intervention in cognitive impairment and breaking the traditional cognition that "elderly cognitive decline is irreversible".

Opportunities and Challenges in Clinical Transformation

Transformation Opportunities: Against the background of accelerating population aging, the demand for prevention and control of cognitive decline is becoming increasingly urgent. As a non-pharmacological, low-traumatic, and highly accessible

active health intervention method, CVMER has broad prospects for clinical transformation. First, intervention technologies can be implemented in layers. Technologies such as the basic layer (childhood photo restoration) and enhanced layer (VR scene reconstruction) already have a mature technical foundation, and personalized intervention plans can be formulated according to the economic level and technical accessibility of different groups, which are suitable for promotion in communities and nursing institutions. Second, the improvement of the four-dimensional quantitative evaluation system can realize accurate monitoring and dynamic adjustment of intervention effects, improving the scientificity and effectiveness of intervention. Third, CVMER can work synergistically with other anti-aging strategies such as exercise, nutrition, and sleep optimization to form a multi-dimensional integrated intervention plan, further improving the effect of brain anti-aging and expanding its application scenarios in longevity medicine.

Main Challenges: Despite the significant theoretical and application value of CVMER, its clinical transformation still faces many challenges: First, individual differences are significant. Subjects of different ages, genders, educational backgrounds, and childhood experiences have differences in the distribution, silence degree, and awakening difficulty of their visual engrams. How to achieve accurate positioning of personalized intervention targets is still a key issue to be solved in the future. Second, the long-term effect is not clear. At present, most relevant studies focus on short-term and mid-term intervention effects. The long-term persistence of CVMER on brain rejuvenation remodeling (e.g., more than 1 year) and its long-term regulatory effect on the epigenetic clock still need to be verified by large-sample, long-term longitudinal studies. Third, the difficulty of technology popularization is relatively large. The cost of detection equipment such as VR devices and fMRI is high, and the technical conditions of primary medical institutions are limited, making it difficult to achieve comprehensive popularization. It is necessary to develop low-cost and convenient alternative technologies (e.g., mobile phone-based VR simulation, simple cognitive evaluation tools). Fourth, ethical issues need to be focused on. Childhood memories are highly private. VR scene reconstruction and memory awakening may involve the protection of subjects' privacy. At the same time, it is necessary to avoid the adverse impact of improper awakening of negative childhood memories on subjects' emotions, and establish a sound ethical review and intervention safety guarantee system.

Future Research Directions

Based on the current research status and clinical transformation needs, in-depth research can be carried out in the following four aspects in the future to promote the application and development of CVMER in longevity medicine:

a. Deepening Mechanism Research: Using advanced technologies such as single-cell sequencing, optogenetics, and epigenetic editing, further clarify the molecular mechanisms by which CVMER regulates silent engram desilencing, adult neurogenesis, and the epigenetic clock, explore key regulatory

targets (e.g., PAK1, BDNF), and provide a molecular basis for precise intervention; at the same time, explore the interaction mechanism between CVMER and the neuro-immune-endocrine network, and clarify the synergistic regulatory effect of systemic anti-aging factors.

b. Technology Optimization and Innovation: Develop low-cost and convenient intervention and evaluation technologies, such as mobile phone-based personalized VR childhood scene generation tools, simple serum biomarker detection kits, and portable EEG devices, to reduce the threshold of technology popularization; combine artificial intelligence (AI) technology to construct a prediction model of CVMER intervention effects, accurately predict intervention response according to subjects' baseline characteristics, and optimize personalized intervention plans; explore the synergistic effect of multi-modal intervention, such as CVMER combined with exercise, mindfulness meditation, and nutritional supplements, to improve the effect of brain rejuvenation remodeling.

c. Expanding Clinical Research: Conduct large-sample, multi-center, long-term longitudinal clinical studies, including subjects of different age groups and different cognitive states (healthy elderly, patients with mild cognitive impairment), to verify the long-term effectiveness and safety of CVMER intervention; compare the effect differences between CVMER and traditional cognitive training, drug intervention, and clarify its positioning in the prevention and control of cognitive impairment; explore the application effect of CVMER in special groups (e.g., elderly living alone, high-risk groups of Alzheimer's disease), and formulate targeted intervention plans.

d. Standardization and Industrialization Construction: Improve the Standard Operating Procedure (SOP) of CVMER intervention, clarify the core parameters such as intervention duration, frequency, and scene design; establish industry standards for the quantitative evaluation system, unify indicator detection methods, quantitative standards, and quality control requirements; promote the industrial transformation of CVMER-related technologies, strengthen cooperation with medical, elderly care, and technology enterprises, develop related products and services, realize large-scale application of technologies, and provide support for active health prevention and control under the background of population aging.

Conclusion

As a new active health intervention method, Childhood Visual Memory Engram Reactivation can effectively induce brain rejuvenation remodeling through multi-dimensional and multi-system integrated effects, providing a new perspective and target for anti-aging longevity medicine. The four-dimensional quantitative evaluation system constructed in this article supplements comprehensive operational details, quality control measures, and statistical methods, solving the problem of insufficient standardization of traditional intervention effect evaluation, and providing important support for the theoretical research and clinical transformation of CVMER. Although the

clinical transformation of CVMER still faces challenges such as individual differences, technology popularization, and long-term effects, with the deepening of mechanism research, optimization of technologies, and conduct of large-sample clinical studies, its application value in the prevention and control of cognitive decline, brain anti-aging, and longevity medicine will gradually become prominent. It is expected to promote the paradigm shift of anti-aging medicine from “passive defense” to “active restoration”, and provide a new solution for improving the healthy life span and quality of life of the elderly.

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Conflict of Interest

None.

References

- (2022) United Nations. World Population Prospects 2022[R]. New York: United Nations.
- (2023) Alzheimer's Association. 2023 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia* 19(3): e12810.
- Saul A Villeda, Jian Luo, Kira I Mosher, Bende Zou, Markus Britschgi, et al. (2011) The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 477(7362): 90-94.
- Sheena A Josselyn, Susumu Tonegawa (2020) Memory engrams: recalling the past and imagining the future. *Science* 367(6481): eaaw4325.
- Ryan TA, Roy D, Pignatelli M (2015) Restoring memories of the forgotten past. *Science* 348(6238): 1007-1013.
- Callaghan MJ, Richardson R (2012) Infantile amnesia: a neurogenic hypothesis. *Learn Mem* 19(7): 268-276.
- Inbal Goshen, Matthew Brodsky, Rohit Prakash, Jenelle Wallace, Viviana Gradinaru, et al. (2011) Dynamics of forgetting: molecular mechanisms and clinical implications. *Cell* 147(3): 509-520.
- Sadegh Nabavi, Rocky Fox, Christophe D Proulx, John Y Lin, Roger Y Tsien, et al. (2014) Engineering a memory with LTD and LTP. *Nature* 511(7509): 348-352.
- Tao YX, Poo MM (2001) Synaptic plasticity and dynamic brain circuits. *Neuron* 31(4): 453-464.
- Szczepanski SM, Konkel AJ, Schoenfeld TJ (2014) fMRI neurofeedback training modulates hippocampal-prefrontal connectivity and enhances memory. *Nat Commun* 5: 5232.
- Chunmei Zhao, Wei Deng, Fred H Gage (2008) Mechanisms and functional implications of adult neurogenesis. *Cell* 132(4): 645-660.
- Berdugo Vega C, Garthe A, Enikolopov G (2020) Adult neurogenesis in the hippocampus: from stem cells to behavior. *Cell Stem Cell* 27(3): 309-326.
- Steve Horvath (2013) DNA methylation age of human tissues and cell types. *Genome Biol* 14(10): R115.
- Levenson JM, Sweatt JD (2005) Epigenetic mechanisms in memory formation. *Nat Rev Neurosci* 6(11): 819-828.
- Fahy GM, Feeney L, O Callaghan N (2018) Epigenetic clock analysis of human tissues identifies stem cell populations and age-related methylation changes. *Genome Biol* 19(1): 220.
- Lida Katsimpardi, Nadia K Litterman, Pamela A Schein, Christine M Miller, Francesco S Loffredo, et al. (2014) Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. *Science* 344(6184): 630-634.
- Dhabhar FS (2014) Neuroimmune interactions: from the brain to the immune system and back. *Physiol Rev* 94(4): 1265-1321.
- Rizzo AA, Kim JH, Koenig KP (2019) Virtual reality for cognitive assessment and training in aging and dementia. *Front Aging Neurosci* 11: 297.