

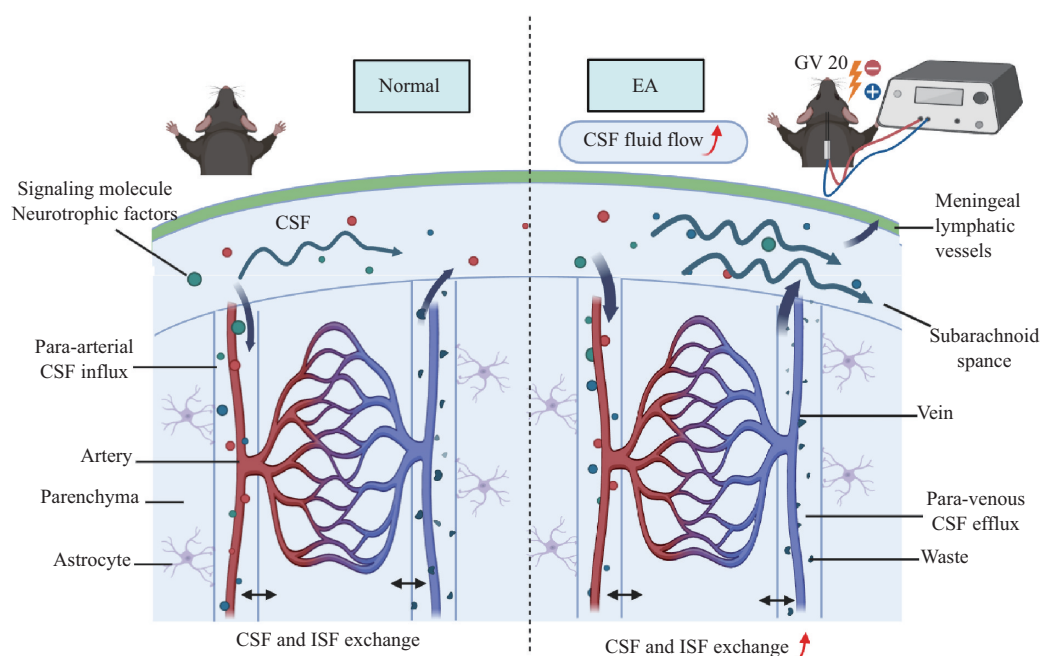


The Specificity of Electroacupuncture at Different Acupoints in Promoting Cerebrospinal Fluid Flow in Mice*

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Graphical abstract



Abstract Objective Cerebrospinal fluid (CSF) plays a crucial role in maintaining the homeostasis of the central nervous system (CNS). CSF rapidly exchanges with interstitial fluid (ISF) *via* the glymphatic system within the brain parenchyma. CSF-ISF circulation and its associated mechanisms are often referred to as the brain lymphatic system. This system is connected directly to meningeal lymphatic vessels (mLVs), jointly performing the function of clearing metabolic waste from the CNS. Emerging evidence indicates that this system is closely associated with the onset and progression of neurodegenerative diseases (NDs) such as Alzheimer's disease (AD). Importantly, abnormal CSF circulation is not only a downstream consequence of AD pathology, but also

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a risk factor. In AD, the dynamics of CSF flow within the CNS are diminished, immune dysregulation occurs, and this may increase the risk of AD by exacerbating the burden of amyloid β -protein ($A\beta$). In the mouse model of AD, impaired CSF flow compromises this clearance function, leading to cognitive deficits. Clinically, acupuncture at cognition-related acupoints is commonly used for the prevention and treatment of AD. However, whether its therapeutic effects are mediated through the modulation of CSF dynamics remains unclear. This study aimed to evaluate the impact of acupuncture on CSF flow and investigate its acupoint specificity.

Methods Mice were randomly assigned to experimental groups for the different electroacupuncture groups with the following acupoints: Baihui point (GV 20), Ear point, Neiguan point (PC 6), and Tianshu point (ST 25). Wild-type mice on a C57BL/6J background were used as controls. Fluorescent tracer was injected into the cisterna magna to label CSF flow. Fluorescence imaging was employed to assess the distribution of CSF within the brain before and after acupuncture stimulation. **Results** Following tracer injection into the cisterna magna, fluorescence signals rapidly reached the cerebellum and medulla—the regions closest to the injection site. Fluorescence intensity was higher in ventral brain regions compared to dorsal regions, likely due to greater vascular density in ventral areas facilitating CSF-ISF exchange. Electroacupuncture at the GV 20 produced the most pronounced enhancement of CSF across the whole brain, while stimulation at the ST 25 primarily augmented flow within subcortical regions. In contrast, electroacupuncture at the Ear point or the PC 6 had no observable effect on CSF in mice. **Conclusion** Electroacupuncture promotes CSF flow into the brain parenchyma in an acupoint-specific manner, with GV 20 exhibiting the most pronounced enhancement of CSF dynamics. These findings suggest that acupuncture-mediated facilitation of CSF flow may represent a potential therapeutic strategy for preventing or delaying age-related cognitive decline.

Key words cerebrospinal fluid, CSF-ISF, electroacupuncture, acupoint specificity

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Cerebrospinal fluid (CSF) is clear, colorless fluid that circulates within the ventricular system, the subarachnoid space, and the central canal of the spinal cord^[1]. Traditionally, it has been regarded as a “cushioning agent”, primarily serving to buffer the central nervous system (CNS) against mechanical impact, facilitate the exchange of nutrients and metabolic waste, and maintain intracranial pressure and homeostasis of the neural microenvironment^[1]. Research over the past decade has demonstrated that CSF is not a static fluid, but rather a key component of a highly dynamic circulatory system involved in metabolic waste clearance, signaling molecule transport, and the regulation of neurodevelopment^[2].

For a long time, CSF circulation was described as a unidirectional flow model: secreted by the choroid plexus, flowing through the ventricles into the subarachnoid space, and finally returning to the venous sinuses *via* the choroid plexus^[3-4]. However, this classical theory struggles to explain certain clinical phenomena, such as the impaired clearance and accumulation of amyloid β -protein ($A\beta$) in the brains of Alzheimer’s disease (AD) patients. In 2012, Iliff *et al.*^[5] challenged this understanding by proposing the glymphatic system, in which CSF enters the brain parenchyma through periarterial spaces, exchanges with interstitial fluid (ISF), and facilitates the clearance of metabolic waste—

including $A\beta$ and tau proteins—*via* perivenous drainage pathways. This process is highly dependent on pulsatile CSF dynamics, particularly during sleep^[6-7]. The discovery established the glymphatic system as the brain’s intrinsic pathway for waste clearance, and its proper function is critical for maintaining cerebral homeostasis.

CSF fills the entire ventricular system, subarachnoid spaces, and perivascular spaces, directly contacting the surfaces and deep structures of most brain regions. It possesses directional flow pathways, and its dissemination speed and methods are unmatched by blood circulation (restricted by the blood-brain barrier) or neuronal projections (point-to-point). With the discovery of the glymphatic system and cerebrospinal fluid-brain parenchyma exchange mechanisms, the continuous flow of CSF serves as a broader, non-synaptic “transport channel” for signaling molecules^[8-9]. This enables the more efficient release and delivery of signaling molecules secreted by specific brain regions to distant target areas, thereby regulating downstream pathways or triggering immune responses^[10].

During embryonic development and early postnatal life, CSF serves as a reservoir of bioactive signaling molecules, rich in morphogens, growth factors, and exosomes released by neural stem cells^[11]. CSF flow establishes spatial concentration

gradients that regulate neurogenesis^[12-13]. Recent studies indicate that CSF dynamics—including pulsatile pressure, directional flow, and associated mechanical forces—can modulate the proliferation and migration of neural precursor cells and influence the division mode of neural stem cells^[14]. These effects are mediated by the synergistic interplay between biochemical cues and biomechanical stimuli within the CSF microenvironment, potentially contributing to cortical organization and neural circuit assembly^[15].

In adults, CSF circulation system maintains a dynamic equilibrium, with the CSF being renewed 3–4 times daily^[16]. This continuous turnover plays a vital role in preserving CNS homeostasis. Any stagnation in CSF flow signifies a disruption of the normal “production-circulation-absorption” dynamic equilibrium. CSF is continuously produced at a rate of approximately 0.3–0.4 ml/min^[17]. When its circulation or absorption is impaired, CSF accumulates within the ventricular system or subarachnoid space, often resulting in elevated intracranial pressure (ICP)^[18]. Moreover, CSF flow—particularly during sleep—drives the glymphatic system, facilitating the clearance of metabolic waste such as A β , tau, and α -synuclein from the brain interstitium^[6-7]. Impaired CSF dynamics may contribute to the accumulation of neurotoxic proteins, potentially accelerating the pathogenesis of neurodegenerative disorders such as AD^[19] and Parkinson’s disease (PD)^[20].

Acupuncture, as a traditional Chinese medical therapy, has garnered increasing attention in modern medical research for its potential in preventing and treating AD and other neurodegenerative diseases (NDs) (such as vascular dementia and PD-related cognitive impairment)^[21-23]. Multiple randomized controlled trials (RCTs) and systematic reviews indicate that acupuncture at acupoints associated with cognitive function can significantly slow cognitive decline in patients with mild to moderate AD^[24-26]. Studies have demonstrated that acupuncture reduces A β deposition^[27] and elevates brain-derived neurotrophic factor (BDNF) levels^[28]. The current effects of acupuncture on the glial lymphatic system and CSF circulation remain unclear. Therefore, we investigated acupuncture’s effects on CSF flow and the acupoint specificity of the “CSF-ISF” exchange system.

1 Materials and methods

1.1 Animals

The 2-month-old wild-type (C57BL/6J) mice with the same genetic background were purchased from specific pathogen free (SPF) (Beijing) Biotechnology Co. Ltd (No. 110324211102475356) and housed in a temperature-controlled animal facility with a 12-h light and dark cycle and free access to water and food. All experimental procedures were approved by the Animal Care and Use Committee of the Beijing University of Chinese Medicine (BUCM-2024070401-3011).

1.2 Electroacupuncture application

Mice were randomly divided into 5 groups ($n=5$): C57BL/6J wild-type (WT), acupuncture at GV 20, acupuncture at Ear point, acupuncture at PC 6, and acupuncture at ST 25. Hair at the acupuncture points was removed prior to needling. Animals were anesthetized using inhaled isoflurane (0.5%–1.5%) *via* a precision vaporizer. Acupuncture was performed using disposable stainless steel Hua Tuo acupuncture needles (0.25 mm $\times$ 13 mm) at the corresponding acupuncture points. The GV 20 is located at the center of the head, at the midpoint of the line connecting the tips of the two ears. The Ear point is situated in the middle and upper third of the auricular cavity. The PC 6 is located on the midline of the forearm, above the median nerve, 3 mm distal to the wrist crease. The ST 25 is located on the anterior midline of the abdomen, at the midpoint of the line connecting the two iliac crests. We applied electroacupuncture with a sinusoidal and continuous wave for 30 min, using an electrical current of 1 mA and a frequency of 10 Hz *via* a stimulator. The intervention was administered twice daily (starting at 9:00 am and 6:00 pm, respectively) for 7 d.

1.3 Intracisternal tracer infusion

CSF flow was assessed by injecting a fluorescent tracer into the cisterna magna. Following anaesthesia, the mouse’s cerebral cistern was exposed and injected with artificial cerebrospinal fluid (aCSF) (#597316, Harvard Apparatus UK) containing 0.5 g/L fluorescein isothiocyanate (FITC)-dextran-3 (Sigma, St. Louis, Missouri). Fluorescent tracers were infused at 1 μ l/min for 5 min. After injection, the needle was kept in place for 15 min. Mice were euthanized at 60 min post-infusion. Brains were collected and fixed

in 4 % paraformaldehyde (PFA) for 24 h.

1.4 Brain collection and frozen section preparation

The fixed brain tissue was placed in a 30% sucrose solution for 24 h. The entire process was conducted at 4°C in the dark. Brain tissue was transferred to a -20°C cryostat (Leica CM3050S) and embedded in SAKURA Tissue-Tek OCT. Sections of 100 µm thick were cut along the sagittal plane. After mounting on slides, the sections were stored in a dark box to prevent fluorescence quenching.

1.5 Image analysis

The prepared frozen sections were placed on a super-resolution Microtissue imaging system (Leica Aperio Versa) and observed using a 10× objective under the FITC (488 nm) channel with a 1 000-ms exposure time. Images were processed using Image Scope (Leica Biosystems) and subsequently analyzed for fluorescence intensity and percentage of fluorescent area *via* ImageJ software.

1.6 Statistical analysis

All data are presented as mean±SEM, and differences between mean values were assessed by one-way analysis of variance (ANOVA) with LSD, as well as Student's *t* test with unpaired two-tailed tests using GraphPad Prism 8.0. *P*<0.05 were considered statistically significant.

2 Results

2.1 Establishment and validation of experimental methods

Following one week of adaptive feeding, mice were randomly assigned to different groups. The acupuncture group received electroacupuncture at GV 20, Ear point, PC 6, and ST 25, respectively. During acupuncture sessions, both the WT group and the acupuncture group underwent anesthesia. Double needles were used to create a loop for local electrical stimulation at the acupoints. After 7 consecutive days of intervention, FITC-dextran-3 was injected into the cisterna magna. FITC-dextran-3, characterized by low molecular mass, excellent water solubility, low toxicity, low immunogenicity, and relative inertness, served as an ideal tracer in this experiment. One hour post-injection, mice were euthanized, cardiac perfused with physiological saline, and brain tissue was collected (Figure 1a, b). To determine electroacupuncture parameters, real-time monitoring

via oscilloscope revealed sinusoidal and continuous waveform stimulation with a 100-ms cycle and 10-Hz frequency (Figure 1c). Multimeter testing confirmed the electroacupuncture current of 1 mA. Identical acupuncture parameters were applied across all the needle groups.

2.2 Electroacupuncture promotes CSF-ISF exchange

To investigate the effects of electroacupuncture on CSF flow, brain tissue samples were collected one hour after tracer injection into the cisterna magna. The distribution of the tracer reflected the trajectory of CSF flow. In the WT group, the tracer was primarily distributed within the cerebellum and medulla oblongata regions. Given the injection site at the cisterna magna, the cerebellum and medulla—being the closest brain areas to the injection point—enabled rapid diffusion. Using the fluorescence distribution in the WT group as a baseline, the acupuncture group demonstrated varying degrees of enhancement in both intraventricular CSF flow and diffusion into the brain parenchyma. The GV 20 group exhibited the most pronounced increase in CSF flow. Fluorescence coverage was extended across all CSF-permeable brain regions, with both fluorescence intensity and distribution area significantly exceeding those of the WT group. The Ear point group, PC 6 group, and ST 25 group also exhibited enhanced fluorescence distribution compared to the WT group. Quantitative analysis of fluorescence area proportion and intensity requires further statistical evaluation. Additionally, within the same group, fluorescence intensity was markedly higher in the ventral brain regions than in the dorsal regions. This difference stems from the denser vascular distribution in the ventral areas (Figure 2).

2.3 CSF-ISF exchange rate exhibits acupoint specificity

To investigate the effects of electroacupuncture stimulation at different acupoints on CSF flow velocity in mice, we delineated multiple regions of interest (ROIs) within the brain based on brain atlas: cerebral cortex (CTX), hippocampus (HIP), subcortical regions (SCR), olfactory bulb (OB), cerebellum (CB), and brainstem (BS) (Figure 3a). We performed quantitative statistical analysis on the average fluorescence intensity and fluorescence area percentage within these ROIs (Figures 3b-f).

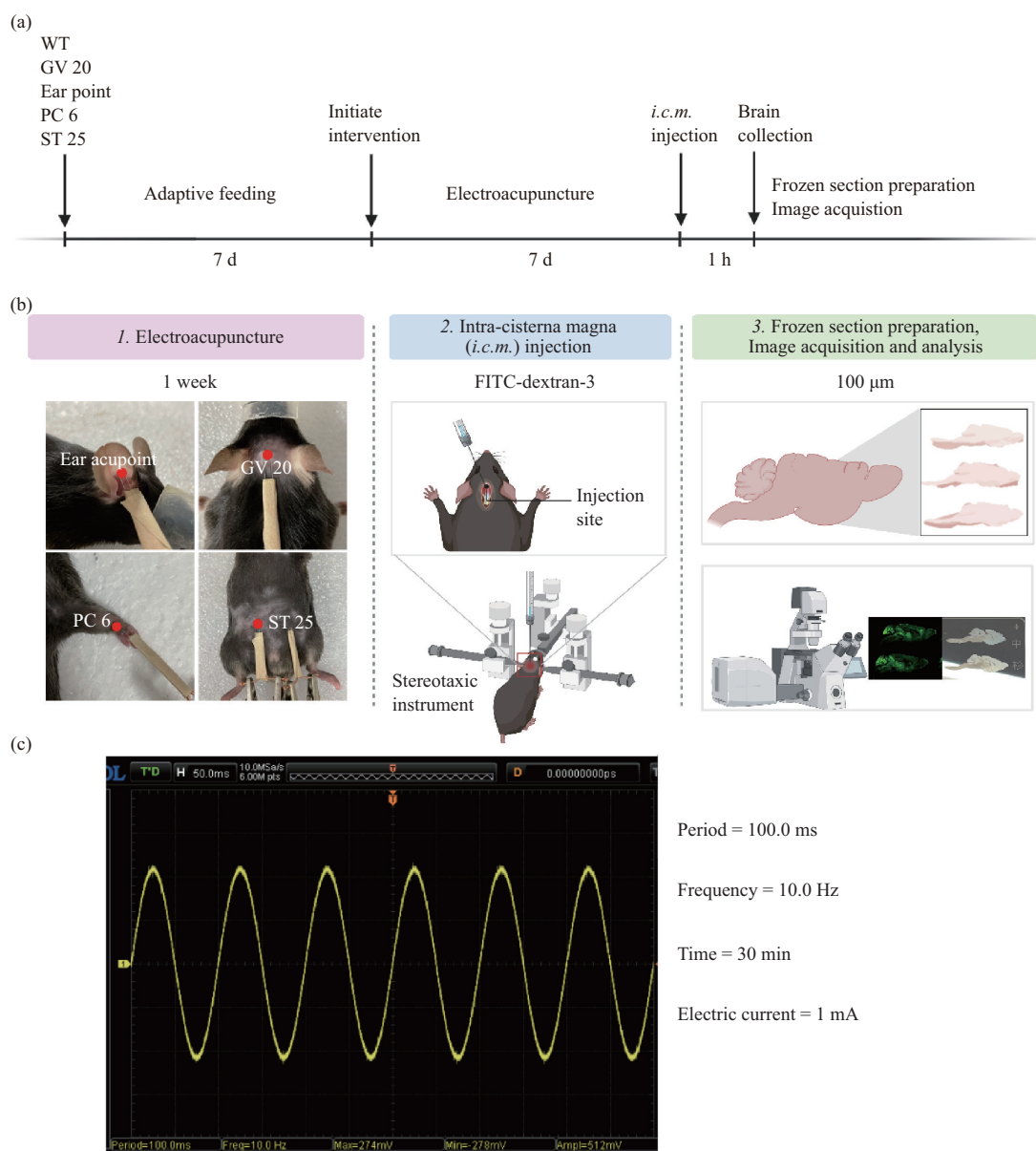


Fig. 1 Establishment and validation of experimental methods

(a) Schematic representation of the protocol. (b) Summary diagram of experimental methods. 1. Electroacupuncture at different acupoint positioning chart, 30 min/d for 1 week. 2. 5 μ l FITC-dextran (3 ku) was injected into the large occipital pool of mice at 1 μ l/min on brain stereotaxis. 3. The mouse brain tissue was sagittally sectioned at 100 μ m using a frozen sectioning machine and then imaged using a fully automated scanning machine. (c) Electroacupuncture parameters: sinusoidal and continuous wave, period 100 ms, frequency 10 Hz, duration 30 min, current 1 mA.

Consistent with the overall observations, the acupuncture group exhibited higher fluorescence intensity and percentage of fluorescent area than the WT group in all regions of interest. Within the same group, the cerebellum showed higher fluorescence intensity than other regions, while the ventral brain regions demonstrated significantly higher fluorescence intensity than the dorsal brain regions

(Figure 3b–f). In the CB region, the fluorescence intensity of the GV 20 group was significantly higher than that of the WT group ($P<0.05$) (b1 in Figure 3b), and the proportion of fluorescent area was slightly higher than in other groups, but no significant difference (b2 in Figure 3b). In the CTX and HIP regions, no significant differences in fluorescence intensity were observed among groups (c1 in Figure

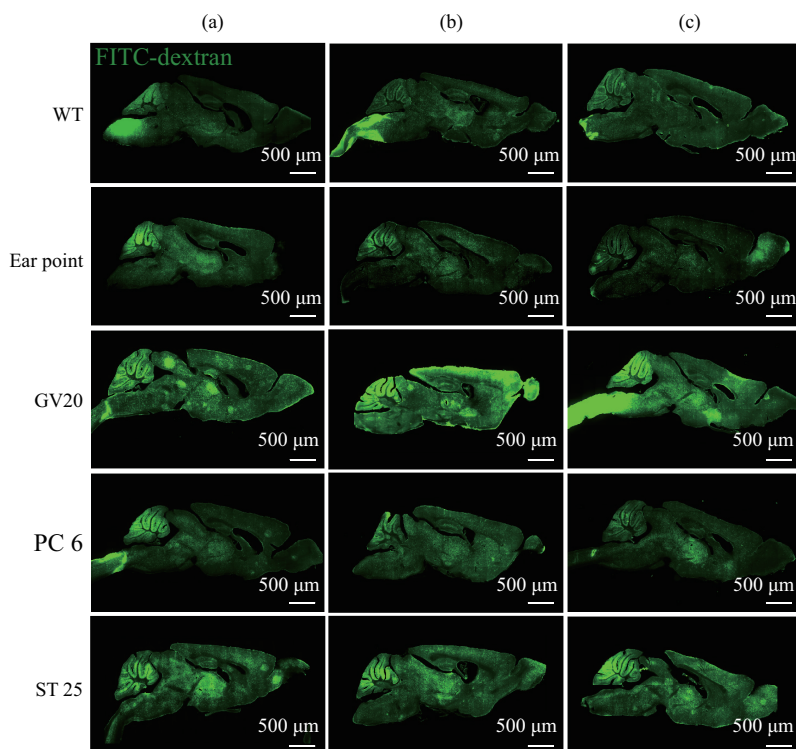


Fig. 2 Representative images of tracer distribution in sagittal brain sections

The mice were divided into 5 groups: WT, Ear point, GV 20, PC 6, and ST 25, with 3–5 mice per group. (a–c) Representative images showing overall tracer penetration observed in sagittal sections (0.48 mm lateral sections) after FITC-dextran-3 injection into the cisterna magna in three mice per group.

3c, d1 in Figure 3d), but the proportion of fluorescent area in the CTX and HIP regions was significantly higher in the GV20 group than in the WT group ($P < 0.05$) (c2 in Figure 3c, d2 in Figure 3d). In the SCR region, fluorescence intensity showed no significant differences among different groups (e1 in Figure 3e), but the fluorescence area percentage of GV 20 and ST 25 was significantly higher than that of WT group ($P < 0.05$; $P < 0.01$) (e2 in Figure 3e). In the OB region, the Ear point group exhibited the lowest fluorescence intensity, 16% lower than the WT (f1 in Figure 3f), while the fluorescence area at GV 20 was significantly higher than the WT group ($P < 0.001$) (f2 in Figure 3f). Electroacupuncture at GV 20 exerts the greatest effect in promoting CSF-ISF exchange velocity.

2.4 CSF diffuses into the brain's parenchyma along its flow pathway

The CSF flow follows a well-defined route, from the lateral ventricles through the foramen of Monro into the third ventricle, then through the aqueduct of Sylvius into the fourth ventricle, and exits *via* foramina of Luschka and Magendie into the

subarachnoid space. Based on our experimental results, after tracer injection into the cisterna magna, fluorescence distribution appeared to varying degrees across different brain regions. The overall distribution pattern aligned with the direction of CSF flow. Based on this, we hypothesize that the tracer diffuses from the cisterna magna to the CB, then flows toward the SCR, subsequently enters the CTX, proceeds to the HIP, and finally reaches the OB (Figure 4).

3 Discussion

This study employed fluorescence tracking and imaging techniques to observe the effects of electroacupuncture at different acupoints on CSF diffusion velocity into brain parenchyma under physiological conditions. It identified the key acupoints with the greatest influence on CSF flow among the commonly used acupoints compatibility in the clinical treatment of NDs: electroacupuncture at the GV 20 demonstrated the most significant effect in promoting CSF flow. Furthermore, CSF flow provides a delivery pathway for therapeutic agents that struggle

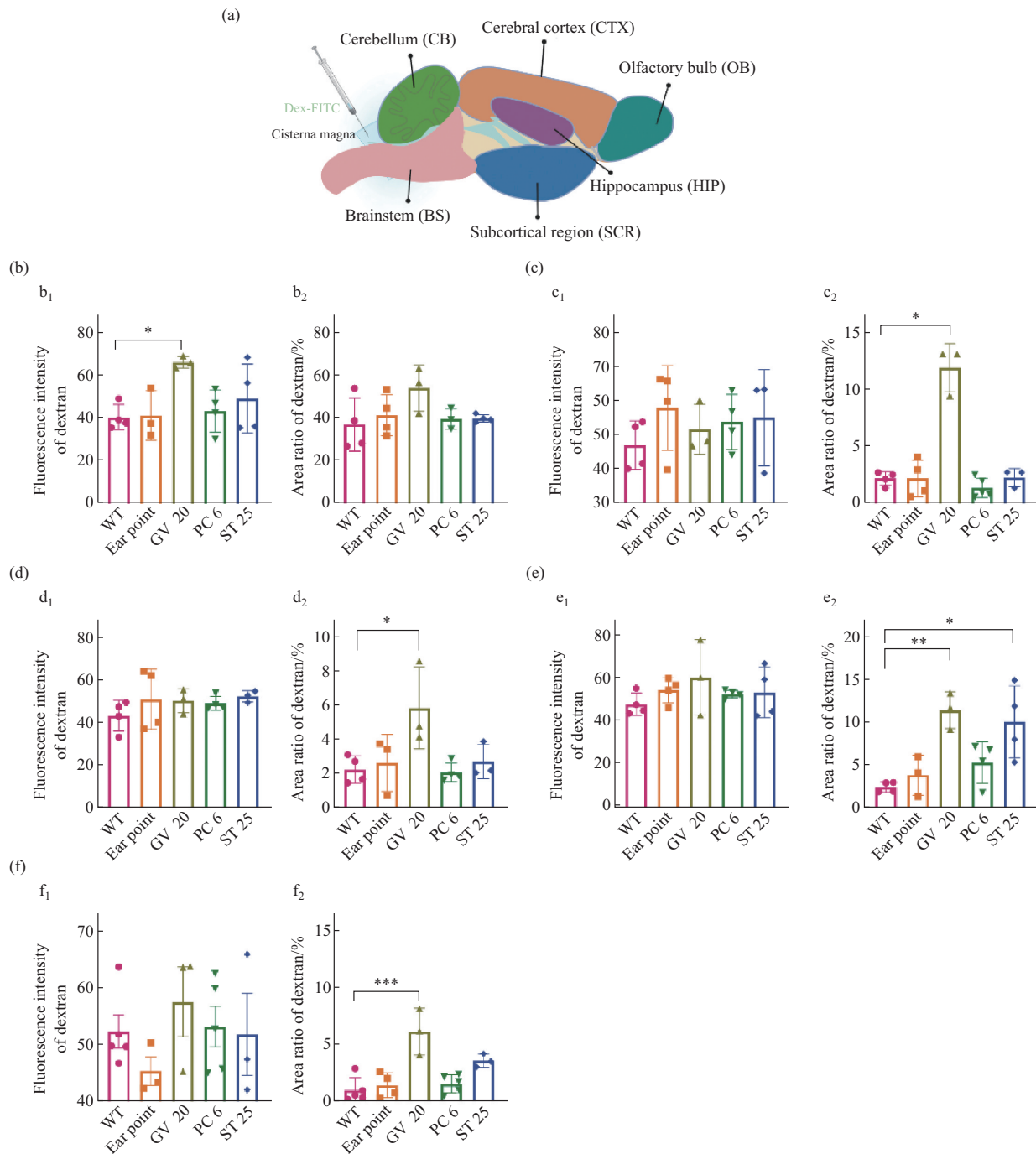


Fig. 3 Quantitative analysis of fluorescence distribution across brain regions following injection into the cisterna magna

(a) Schematic diagram of cisterna magna injection and brain region delineation. (b–f) Average fluorescence intensity and percentage of fluorescent area in the CB (b), CTX (c), HIP (d), SCR (e), and OB (f) ($n=3-5$, $*P<0.05$, $**P<0.01$, $***P<0.001$, using unpaired Student's t test). CB: cerebellum; CTX: cerebral cortex; HIP: hippocampus; SCR: subcortical regions; OB: olfactory bulb.

to penetrate the blood-brain barrier (BBB) [29–30]. However, this study was conducted in healthy young mice and has yet to be validated in AD model mice, laying the groundwork for subsequent pathological research.

With the confirmation of the glymphatic system and mLVs, studies have revealed that CSF can rapidly exchange with ISF through the glymphatic system within brain parenchyma. This glymphatic system connects directly to mLVs *via* lymphatic vessels in the

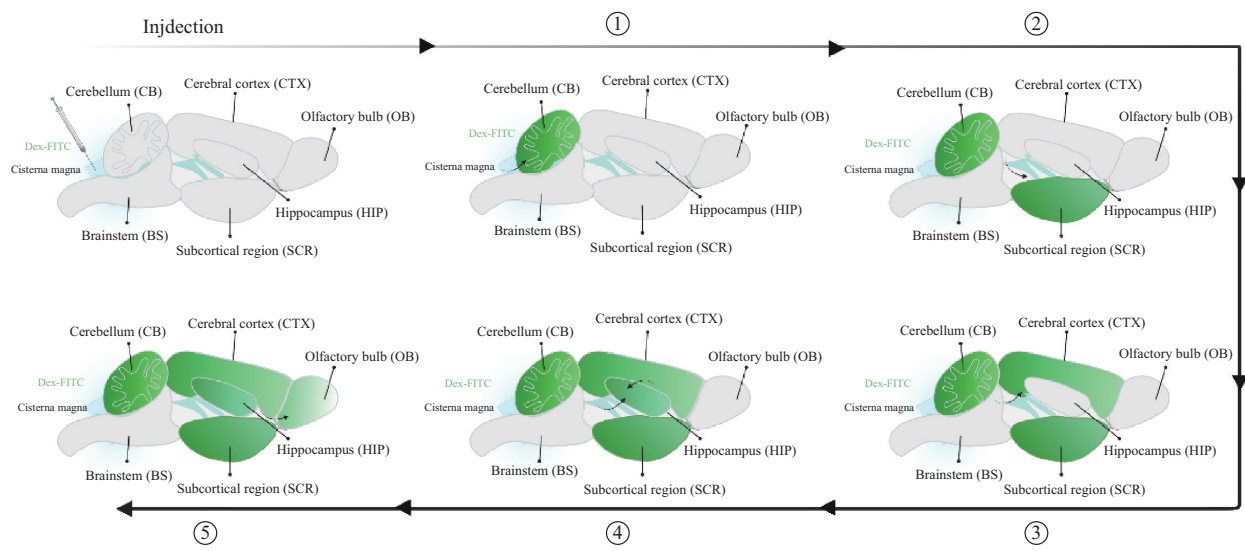


Fig. 4 Schematic diagram of the sequence of CSF diffusion into the parenchyma

cavernous sinus (CAV) region. CSF in the subarachnoid space connects directly to mLVs *via* the arachnoid sleeves and lymphatic endothelial cells (LECs) within the arachnoid granules^[31]. These interconnected systems exhibit diminished CSF dynamics, immune dysregulation, elevated glial proteins associated with AD genetic risk factors and anti-inflammatory states, and continuous patrolling and clonal expansion of antigen-specific CD8⁺ T cells in the early stages of AD^[32-34]. In the CSF system of aged mice, loss of aquaporin 4 (AQP4) polarization function at astrocytic terminal foot processes around blood vessels impedes effective CSF flow into parenchymal tissues^[35-38].

The enhancement of CSF flow velocity following acupuncture at the GV 20 may be related to its anatomical location. Located at the vertex of the head, the GV 20 is accessed by inserting the acupuncture needle along the cranial surface, directly stimulating the cranial bone. Immediately beneath lies the mLVs within the dura mater. The cranial bone connects to the dura mater, and cellular communication exists between bone marrow and the dura mater. The arachnoid sac opening leads to the dura mater, while the subarachnoid space is filled with cerebrospinal fluid^[39]. Beneath the meninges lies the cerebral cortex, connected to the meninges *via* the pontine veins. The perivascular glymphatic system surrounding cortical arteries and veins facilitates rapid exchange between ISF and CSF. Stimulation signals

generated by acupuncture may transmit through these anatomical pathways, acting on AQP4 aquaporin in the terminal processes of astrocytic cells within the glymphatic system, thereby regulating CSF flow. The regulatory pathway of electroacupuncture on the glymphatic system remains unclear and warrants further investigation.

This study has the following limitations: while observing the fluorescence intensity of the tracer diffusion area into brain parenchyma under different electroacupuncture point conditions can generally describe CSF flow, it cannot precisely distinguish whether electroacupuncture increases overall CSF flow volume or optimizes perfusion efficiency or drainage pathways. The absence of a sham-needle group overlooks the potential for electroacupuncture stimulation itself to induce systemic physiological responses. These non-specific factors may confound the “specific” regulation of the CSF system. Future studies will refine control group design by incorporating a sham-needle group and monitoring blood pressure to distinguish non-specific influences on CSF dynamics. Additionally, alterations in vascular tight junction proteins will be assessed to determine whether vascular permeability is affected.

4 Conclusion

The spatiotemporal dynamics of CSF-ISF exchange vary across brain regions, exhibiting a spatial gradient along established CSF flow pathways.

Moreover, CSF flow velocity shows differential modulation depending on the acupoint stimulated. Electroacupuncture at GV 20, Ear point, PC 6, and ST 25 all enhanced CSF flow velocity in the brains. Notably, electroacupuncture at GV 20 significantly increased CSF influx into the brain parenchyma, suggesting its potential as a novel strategy for the prevention or treatment of neurological disorders such as AD, PD, and stroke.

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电针刺激小鼠不同穴位促进脑脊液流动的特异性*

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摘要 目的 脑脊液在维持中枢神经系统稳态中发挥关键作用, 其与间质液通过胶质淋巴系统进行快速交换, 二者循环及相关机制被称为脑淋巴系统。该系统与脑膜淋巴管直接连通, 共同介导中枢神经系统代谢废物的清除。近期研究表明, 脑淋巴系统功能与阿尔茨海默病等神经退行性疾病的发生发展密切相关。值得注意的是, 脑脊液循环异常不仅是阿尔茨海默病病理过程的下游表现, 也构成其潜在风险因素。阿尔茨海默病患者中枢神经系统内脑脊液流动减弱, 伴随免疫调节紊乱, 可能通过加剧 β 淀粉样蛋白沉积负荷而升高发病风险。在阿尔茨海默病小鼠模型中, 脑脊液流动受损可削弱清除功能, 进而加重认知缺陷。临床上, 针刺认知相关穴位常被用于阿尔茨海默病的防治, 然而其疗效是否通过调节脑脊液动力学实现尚不明确。本研究旨在评估针刺对脑脊液流动的影响, 并探讨其穴位特异性。**方法** 将小鼠随机分组, 分别予电针刺激百会、耳穴、内关及天枢穴, 并将C57BL/6J背景野生型小鼠作为空白对照。经枕大池注射示踪剂标记脑脊液流动, 采用荧光成像技术评估针刺前后脑脊液在各脑区的扩散情况。**结果** 示踪剂注入枕大池后, 荧光信号迅速抵达邻近注射点的小脑与延髓区域。腹侧脑区荧光强度高于背侧, 可能与腹侧血管密度较高, 脑脊液与间质液交换更为活跃有关。电针百会穴对全脑范围内脑脊液流动的增强效应最为显著, 电针天枢穴则主要促进皮层下区域脑脊液流动, 而电针耳穴与内关穴对小鼠脑脊液流动均未观察到明显影响。**结论** 电针可促进脑脊液流动并向脑实质扩散, 且呈现穴位特异性, 其中电针百会穴增强脑脊液流动的作用最为突出。针刺介导的脑脊液流动调节或可成为预防与延缓年龄相关认知衰退的潜在治疗策略。

关键词 脑脊液, 脑脊液-间质液, 电针, 穴位特异性

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