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Acupuncture in Neuroinflammation Regulation May be Related to the Inhibition of M1 Microglial Activation Involved in Dementia*

TAN Yan[1)**], ZHANG Ya-Li[2)], ZHANG Jia-Ni[2)], BAI Wan-Zhu[3)**]

([1)]*School of Life Sciences, Beijing University of Chinese Medicine, Beijing* 100029, China;
[2)]*School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing* 100029, China;
[3)]*Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing* 100700, China)

Abstract Acupuncture is an ancient and important part of traditional Chinese medicine. As a non-pharmacological intervention recommended by the World Health Organization (WHO), acupuncture is widely used in the treatment of a variety of diseases. A large number of clinical and experimental evidences show that acupuncture can improve cognition by regulating neuroinflammation. Inflammation is a common pathological reaction of many neurodegenerative diseases, such as the activation of glial cells, the increase and release of inflammatory factors. Currently, a great deal of work progresses in the field of acupuncture in the field of anti-inflammation. To summarize the role of acupuncture in improving neuroinflammation in dementia, this review focuses on brain diseases and discusses the mechanism of acupuncture in the activation of glial cells in Alzheimer's disease (AD), vascular dementia (VD), Parkinson's disease (PD). Those acupoints distributed in 14 meridians and concentrated in the head and the distal extremities, are closely related to the activation and regulation of microglia. As described by recent studies, the inhibition of M1 microglial activation mediated by TLRs/NF-κB and MAPKs pathways may be one of the key mechanisms of acupuncture regulating neuroinflammatory response and improving cognitive impairment in AD, VD and PD.

Key words acupuncture, dementia, microglia, neuroinflammation
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Acupuncture is an ancient and vital part of traditional Chinese therapy with minimal side effects. Acupuncture needle inserted at the specific acupoint stimulates humoral immune response and induces endocrine, neuroendocrine, autonomic, and systemic behavioral responses through the local reflex and the central nervous system (CNS)[1]. It has been widely practiced in China over 3 000 years and accepted in the West for treating a list of ailments, including pains, cardiovascular diseases, and many diseases proved by a number of high-quality clinical evidence[2-5]. There are two main types of acupunctural methods: manual acupuncture (MA) and electroacupuncture (EA).

MA involves the needle penetration at specific stimulation acupoints along the surface of body, followed by manually twisting or thrusting; EA is a technique in which two needles are inserted to produce electric current[6].

Currently, with progress in evidence-based medicine and clinical epidemiology, more randomized, controlled trials (RCTs) and meta-analyses have been conducted to evaluate the efficacy

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** Corresponding author.
TAN Yan. Tel: 86-10-53912152
E-mail: yantan@bucm.edu.cn, yantan828@163.com
BAI Wan-Zhu. Tel: 86-10-64089390
E-mail: wanzhubaisy@hotmail.com
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of acupuncture as an alternative therapy in CNS disorders, such as stroke, spinal, cord injury, and dementia. Neuroinflammation is not only a common phenomenon in CNS disorders, but it is involved into the pathological processing. In addition, a great deal of work has been accumulated in the field of acupuncture in the field of anti-inflammation[7]. Therefore, due to illustrate the mechanism of acupuncture on dementia, we mainly focus on AD, VD and PD, and try to speculate its regulation of microglia activation, since glial-mediated neuroinflammation, especially microglial cells (the tissue macrophage population of the brain), has an indispensable impact on the brain[8].

1 The efficacy of acupuncture in dementia

Accompanied with aging of the population, age-related diseases, especially neurodegenerative disorders, become worldwide challenges. For three forms of dementia, AD, VD and PD, the definitive treatment is still absent at present. Since 2003, there is no new drug approved for the treatment of AD, though there are two promising drugs under further clinical investigations (Aducanumab from Biogen and Eisai, GV-971 from Green Valley). In China, as an alternative therapy in neurodegenerative diseases, the aim of acupuncture treatment is to control symptoms with few side effects.

1.1 In clinic, acupuncture treatment improves cognitive functions and other related symptoms relevant to dementia

AD is the most common form of dementia, which accounts for nearly 80% of dementia. It affects one-fifth of those aged over 85 years. Almost all the drugs are failed or do not meet the end of efficacy in clinic [9]. Besides, a number of studies have shown that acupuncture benefits memory, learning, and the brain functions. In an RCT study, acupuncture treatment three times per week for 4-week obviously decreased AD assessment-cognitive section (ADAS-cog) scores with no adverse events[10]. In combination with donepezil, acupuncture showed more effective than donepezil alone at improving the mini-mental state examination (MMSE) score[11]. In combination with herbal medicine, a systematic review showed that the combination was more effective at improving MMSE and traditional Chinese medicine (TCM) symptoms[12], such as menopausal insomnia[13], liver Qi stagnation[13]. By brain imaging technologies, EA at GV20 induced increased regional hemodynamic in the orbital frontal cortex, middle cingulate cortex, precentral cortex and precuneus, which indicated that EA at GV20 may induce a specific pattern of neural responses. In addition, acupuncture at ST36 pronounced insula and secondary somatosensory cortex BOLD activation, and increased ALFF in the cerebral cortex, brainstem, cerebellum[14].

VD is another major form of dementia, being responsible for around 15% of all dementia patients[15]. In general, it refers to problems with reasoning, planning, judgment, memory and other thought processes caused by brain damage from impaired blood flow to the brain. As alternative therapy in the pragmatic trial, Liu's team revealed that MMSE, Activities of Daily Living (ADL) score were significantly reduced under acupuncture treatment, suggesting beneficial effects on improving cognitive functions of acupuncture in VD patients[16].

PD is the most common motor disorder and the second most common neurodegenerative disorder, affecting 1%−2% of population older than 60 years. The pathogenesis of PD may be related to environmental factors, immunological abnormalities, mitochondrial dysfunction and oxidative stress. Like AD, the pathogenesis of PD is still unclear, but it is considered that PD has a close relationship with the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta of the brain[17-18]. In addition to standard treatments, complementary and alternative medicine has been administrated in clinic[19]. As one of the most popular alternative therapy, acupuncture relieves some motor symptoms in PD patients, and markedly improves many non-motor symptoms such as psychiatric disorders, sleep problems, and gastrointestinal symptoms[20]. Additionally, some studies have demonstrated that acupuncture could improve therapeutic efficacy and reduce side effects or complications induced by drugs such as nausea and vomiting[21], chemotherapy-induced peripheral neuropathy[22], *etc*.

1.2 *In vivo*, acupuncture intervention improves cognitive functions and reduces neuroinflammation relevant to dementia

With the extensive use of acupuncture in dementia, the efficacy based on animal model of the intervention was widely investigated.

Among the different acupoints, the utility of GV20 is a valuable acupoint to suppress amyloid β (Aβ) generation, improve glucose metabolism and attenuate neuropathological features in AD-like animal models[6]. In APP/PS1 transgenic mice, scalp acupuncture improved their spatial memory and learning; the glucose metabolism is up-regulated in the hippocampus[23]. In SAMP8 mice, acupuncture at GV20, GV26, and GV29 significantly reduced the expression of IL-1β, NLRP3 inflammasome in the hippocampus[24]. Combined with donepezil, the efficacy of acupuncture was outperformed in improving spatial learning and memory compared with donepezil treatment alone[25].

In the cerebral ischemia models, acupuncture could reverse long time potentiation (LTP) impairment with a six day of EA intervention by inducing neural plasticity in rodents[26-27]. In a systematic review, acupuncture may have an effective effect in improving cognitive function in VD animal models; the mechanisms refer to anti-apoptosis, anti-oxidative stress reaction, and metabolism enhancing of glucose and oxygen[28]. Additionally, acupuncture increased pyramidal neuron number in the hippocampal CA1 area, and reduced oxidative stress, Nuclear factor-kappa B (NF- κB) activation in the cerebral multi-infarct rats[29-30].

As described[19], acupuncture is able to improve motor function and enhance dopamine availability in 6-OHDA-lesioned PD mice; EA increased the latency to fall from the accelerating rotarod, improved striatal dopamine levels in the PD model and reduced neuroinflammation[31-32]. In Parkinsonian rhesus monkeys, the chronic acupuncture treatments could significantly improve the movement speed and the fine motor performance time during the period of intervention, and the effect could be detected even after 3 months[33]. In addition, a systematic review of animal studies addressed that acupuncture exerts a protective effect on dopaminergic neurons in rodent models of PD[17]. Besides the efficacy, acupuncture could reduce the dosage of levodopa and ameliorate drugs-induced side effects or complications[1].

1.3 The acupoints for the treatment of dementia is mainly distributed on 14 meridians

Based on theories of TCM and clinical practices, we found that the acupoints distributed on 14 meridians, concentrated in the head and the distal extremities, were closely related to the treatment of dementia[6,34]. For the treatment of AD, 24 acupoints are located on 11 meridians, such as *Dumai* (GV), *Renmai* (CV), *Pangguangjing* (BL), *Ganjing* (LR), *Danjing* (GB), *Shenjing* (KI), *Weijing* (ST), *Pijing* (SP), *Xinjing* (HT), *Xinbaojing* (PC), and *Sanjiaojing* (TE). The selection of acupoints for the treatment of VD is similar to AD's, while it is a bit different from PD. For VD, there are main 19 acupoints located on 9 meridians, which are DV, CV, BL, LR, GB, KI, ST, SP, and *Xinbaojing* (PC). For PD, 23 acupoints are located on 10 meridians. There are ST, SP, KI, LR, GB, BL, PC, *Dachangjing* (LI), *Xiaochangjing* (SI) and *Feijing* (LU) (Table 1). We also found that the meridians of GV and ST play an important role in all these three forms of dementia. GV belongs to one of eight extraordinary meridians, which communicates with the other meridians to maintain the inner balance. It originates from the brain, goes through the middle of the back and ends in the perineum. According to TCM, GV has a close relationship with the brain function. The crucial acupoint on GV, GV20 (*Baihui*), locating on the top of the head, refers to coordinate with many meridians, resulting in improving the learning and memory capability[1-2]. ST is one of the twelve meridians of human body. It distributed on the front of the human body, which runs through the whole body, starting from the eye areas to the foot. It is mainly used to treat digestive system, nervous system, respiratory system, and circulatory diseases. ST36 is one of the most famous acupoints on ST. *In vivo*, EA at ST36 can rescued sepsis mice by inducing a vagal activation of releasing dopamine in the adrenal medulla[35]. In addition, several researches illustrated that acupuncture at both GV20 and ST36 improved memory deficits in VD rats and ischemic stroke model[2,36].

Furthermore, according to the clinical study of *Acu-Reflex Point Acupuncture*, Jin's team proposed that the surface of human body exists central reflex area, which is consistent with the theory of meridians[37]. Generally, from the viewpoint of effective control, CNS controls and coordinates the left and right parts of the body, its anatomical position must be located in the midline of the body. The central reflex area is located in the center of the midline of body (the meridians of GV and CV) and in the middle or boundary between the body reflex area and the

Table 1 The comparison of acupoints distributed on 14 meridians in the treatment of AD，PD and VD

AD			VD			PD		
Meridians（In Chinese）	Acupoints	In Chinese	Meridians	Acupoints	In Chinese	Meridians（In Chinese）	Acupoints	In Chinese
GV（*Dumai*，督脉）	GV14	*Dazhui*	GV	GV14	*Dazhui*	LI	LI4	*Hegu*
	GV20	*Baihui*		GV20	*Baihui*	（*Dachangjing*，大肠经）	LI5	*Yangxi*
	GV24	*Shengting*		GV24	*Shengting*		LI11	*Quchi*
	GV26	*Shuigou*		GV26	*Shuigou*		LI15	*Jianyu*
	GV29	*Yintang*					LI20	*Yingxiang*
CV（*Renmai*，任脉）	CV4	*Guanyuan*	CV	CV6	*Qihai*	SI	SI3	*Houxi*
	CV6	*Qihai*		CV12	*Zhongwan*	（*Xiaochangjing*，小肠经）	SI6	*Yanglao*
	CV12	*Zhongwan*		CV17	*Danzhong*	LU（*Feijing*，肺经）	LU5	*Chize*
	CV17	*Danzhong*						
ST（*Weijing*，胃经）	ST25	*Tianshu*	ST	ST25	*Tianshu*	ST	ST7	*Xiaguan*
	ST36	*Zusanli*		ST36	*Zusanli*		ST36	*Zusanli*
	ST40	*Fenglong*		ST40	*Fenglong*		ST41	*Jiexi*
							ST42	*Chongyang*
KI（*Shenjing*，肾经）	KI3	*Taixi*	KI	KI1	*Yongquan*	KI	KI3	*Taixi*
	KI4	*Dazhong*					KI7	*Fuliu*
							KI10	*Yingu*
BL	BL17	*Geshu*	BL	BL17	*Geshu*	BL	BL40	*Weizhong*
（*Pangguangjing*，膀胱经）	BL23	*Shenshu*		BL20	*Pishu*			
				BL23	*Shenshu*			
SP（*Pijing*，脾经）	SP6	*Sanyinjiao*	SP	SP6	*Sanyinjiao*	SP	SP3	*Taibai*
	SP10	*Xuehai*		SP10	*Xuehai*		SP6	*Sanyinjiao*
							SP9	*Yinlingquan*
LR（*Ganjing*，肝经）	LR3	*Taichong*	LR	LR3	*Taichong*	LR	LR3	*Taichong*
GB（*Danjing*，胆经）	GB39	*Xuanzhong*	GB	GB20	*Fengchi*	GB	GB30	*Huantiao*
							GB34	*Yanglingquan*
PC	PC6	*Neiguan*	PC	PC9	*Zhongchong*	PC	PC3	*Quze*
（*Xinbaojing*，心包经）								
HT（*Xinjing*，心经）	HT7	*Shenmen*						
TE	TE5	*Waiguan*						
（*Sanjiaojing*，三焦经）								

visceral reflex area. According to clinical studies, the most frequently used acupoints in AD, PD and VD are displayed in Figure 1.

2 The neuroinflammation regulation of acupuncture in dementia

Neuroinflammation is common in almost all forms of dementia. In brains, its micro-environment is mainly composed of neurons and glial cells, the latter of which accounts for nearly 80% of neuronal cells, not only provides functional supports for neurons but also the primary defense line of the CNS[38]. Microglia, accountingt about 10%−15% of all the glial cells, generally belongs to resident innate immune system of CNS. Cytokines are considered constitutive factors of the brain where they are mainly expressed in microglia and astrocytes[39]. In addition, an accumulating evidence demonstrates that glial-mediated neuroinflammation, especially microglial cells (the tissue macrophage population of the brain), has an indispensable impact on the brain[8].

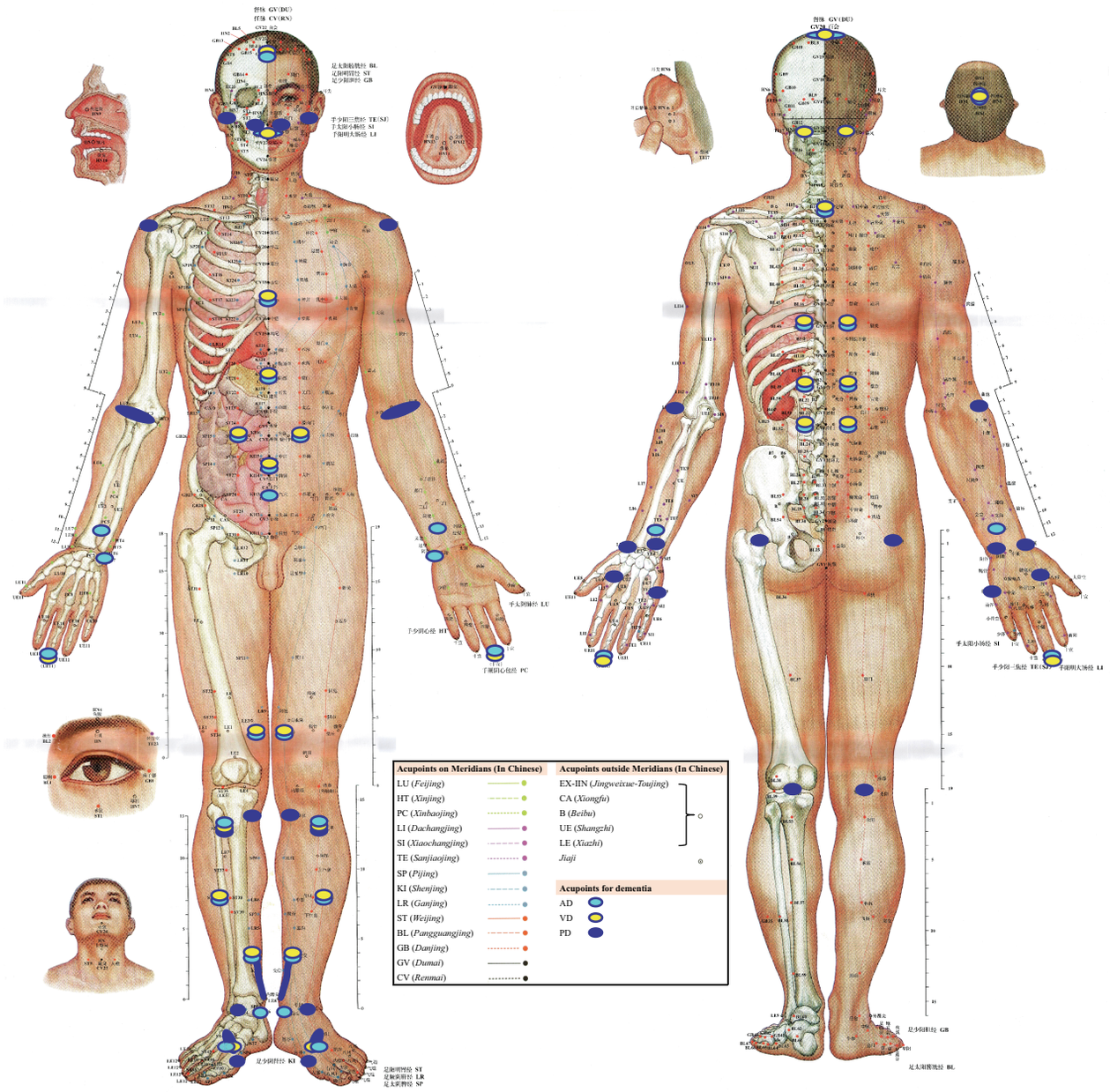

Fig. 1　The distribution of acupoints mainly in AD，PD and VD

2.1　M1 phenotype microglial activation is mostly involved into neuroinflammation relevant to dementia

Microglia, as the main participator in CNS, surveys the brain and rapidly responds to stress or damages. Under physiological conditions, microglia actively contribute to synaptic plasticity and circuit functions. However, under pathophysiological conditions, activated microglia is a "double-edged sword", by performing several macrophage-like immune functions. Once activated, microglia can adopt diverse phenotypes ranging between two extremes: a classically activated M1 phenotype that is involved in pro-inflammatory actions, such as cytokine release, phagocytosis, and an alternative activated M2 phenotype that is crucial to anti-inflammatory response, angiogenesis and tissue repairmen[40] (Figure 2).

In the pathological processing of AD, neuroinflammation plays a significant role in the mechanisms of AD's onset and progression[41]. In an

early event during AD pathophysiology, overall inflammation or Aβ triggers an inflammatory response and microglial release of neurotoxic cytokines; during the processing, the balance of activated microglia is out of control that a vicious cycle of primed microglial occurred to release proinflammatory factors that promoted neuronal damages and neuronal dysfunction under a chronic stress[42]. Primed microglia can induce the production of Aβ, tau pathology, neuroinflammation, leading to the damage of neuron functions[43]. In the postmortem analysis of AD brains, a massive reactively M1 microglia co-localized with amyloid plaques. Almost all the cytokines, for example, IL-1β, IL-6, TNF-α, and IL-8 are increased in AD subjects compared to the controls[44-45]. In AD transgenic model, microglia accumulation within white matter was correlated with cognitive deficits in an age-dependent[46]. Several signaling pathways are related with microglia activation, such as MAPK signaling, NF-κB pathway, mTOR signaling, Rho/Rho kinase pathway, NOTCH signaling, GSK3 signaling[47].

A growing evidence of clinical studies suggested a close link between VD and inflammatory changes of white matter with chronic cerebral hypoperfusion. Inflammatory factors, such as interleukins (ILs), matrix metalloprotease (MMP), TNF-α, Toll-like receptor 4 (TLR4) in microglia caused white matter damage, leading to neurodegeneration, and exacerbated neuroinflammation[48]. In VD patients, it has been found that neuroinflammation is induced by microglial activation through TLR4, accompanied with high levels of proinflammatory cytokines. Touil-Boukoffa's team addressed that the onset of necroptosis in hippocampus was mediated by TLR4/NF-κB signaling in M1 microglial activation with higher production of TNF-α, IL-1β, and protein expression of p65, MMP9, iNOS[49].

PD refers to the second most common neurodegenerative disorder after AD, and characterizes by classical parkinsonian motor symptoms because of dopamine deficiency within the basal ganglia[50]. Although the etiopathogenesis of PD remains unclear, neuroinflammation in PD is a process that occurs alongside the loss of dopaminergic neurons, and is associated with alterations to many cell types. Activated by an FCγ receptor pathway, microglia subsequently causes substantia nigra cell injury[51]. There are increased pro-inflammatory mediators in the striatum and substantia nigra, including TNF, IL-1β, IL-6, inducible nitric oxide synthase (iNOS) and cycloxygenase-2 (COX-2). A significant increase levels of cytokines, such as IL-1β, IL-2, IL-6 and TNF in the substantia nigra and cerebrospinal fluid (CSF) have been observed in PD patients[50].

Therefore, in order to ameliorate the pathological performances, it is crucial to modulate the balance of M1 and M2 microglial activation by inhibiting M1 phenotype in dementia.

2.2 Acupuncture can inhibit M1 phenotype microglial activation by a variety of pathways

Since its public acceptance and good efficacy, increasing attention has been now paid to exploring the mechanisms of acupuncture in neuroinflammation regulation[52]. However, there is few studies on acupuncture and microglia modulation in dementia. Based on other CNS related disorders, breakthroughs have been made in the signaling pathway of acupuncture by inhibiting microglia, which could indicate the modulation pathway of acupuncture in dementia as they selected similar acupoints[41].

Neuroinflammation is considered as a key pathogenesis of postoperative cognitive dysfunction (POCD), accompanied with microglial activation and high levels of pro-inflammatory cytokines in the brain. In aged POCD rats, Wang's team found that EA significantly improved the spatial memory that rats spent more time in the target quadrant; EA inhibited microglial activation with a reduced level of pro-inflammatory cytokines, as well as the protein expression of TLR2 and LTLR4 in the hippocampus[53]. In the astrocytic α-synuclein mutant mouse model, acupuncture improved the movement and prevented the loss of dopaminergic neurons by inhibiting microglial activation[54]. In the model of septic brain injury, Zhou's team administrated the pre-intervention of EA. EA significantly decreased the levels of TNF-α, IL-6, malondialdehyde (MDA); again, the microglial activation was inhibited by EA with downregulation of TLR4, NF-κB[55]. In middle cerebral artery occlusion (MCAO) rats, TLR4/NF-κB signaling pathway in microglia was inhibited by EA[56]. Other CNS disorders, such as spinal cord injury (SCI), Yune's team found that EA facilitated significant function recovery by inhibition p38MAPK and ERK signaling in microglia[57-58]. Additionally, in PD-like mice, acupuncture significantly reduced the

expression of COX-2, iNOS and macrophage antigen complex-1 (MAC-1), the key surface marker of M1 microglia[32]. Medeiros's team illustrated that bee venom injection at ST36 and GV3 reduced inflammatory markers and reduced the polarization of the microglia M1 phenotype marker (iNOS) and increased microglia M2 phenotype markers, such as Arg-1 and TGF-β in the model of SCI[59].

Furthermore, triggering receptor expressed on myeloid cells 2 (TREM2) is a microglia-specific receptor in the CNS that is involved in regulating neuroinflammation in cerebral ischemia[4]. EA suppressed neuroninflammation in the brain, the effect of which was reversed by TREM2 silencing through PI3K/Akt and NF-κB signaling[60-61]. By inhibition microglial activation, acupuncture can modulate neuroinflammation by TLRs pathway, MAPKs pathway, BDNF-TrkB pathway, PI3K/Akt pathway. TLRs play an important role in the innate immune response, and emerging evidence indicates their role in neurodegeneration[62]. TLR4 can cause a series activation of downstream inflammatory factors, resulting in the activation of NF-κB signaling in microglia, the latter of which is responsible for neurotoxic processes in dementia[55,63-64]. Liu's team proposed that it was important to inhibit microglial over-activation by attenuating TLR4/NF-κB signaling[15]. TLR4 antagonists could be an ideal candidate for the therapeutic strategy in dementia[49]. Together, the effects of acupuncture in neuroinflammation regulation can be modulated by inhibiting M1 microglial activation by a variety of pathways (Table 2).

Table 2 Effects and mechanisms of acupuncture via inhibiting microglial activation in CNS−related diseases

Acupoints	Medrian	Type	Model	Efficacy of acupuncture	Effect on inflammation-related factors	Effect on microglia	Signaling pathway	Ref.
GV20, GV14	*Dumai*	EA	Aged	Spatial memory ↑	TNF-α ↓ IL-1β ↓ IL-6 ↓ HGMB1 ↓ TLR-4/2 ↓	M1 Activation ↓	Microglia/TLRs pathway	[53]
GV20 ST36	*Dumai* *Weijing*	EA	Septic brain injury	Survival rate ↑ Cognitive function ↑ Encephaledema ↓ Brain injury ↓ Neuronal apoptosis ↓	TNF-α ↓ IL-6 ↓ SOD ↑ MDA ↓ NF-κB ↓ TLR-4 ↓	M1 Activation ↓	TLR-4/NF-κB pathway	[55]
GV26 GB34	*Dumai* *Danjing*	MA	Spinal cord injury	Functional recovery ↑ Apototic cell death of neurons ↓ Apototic cell death of oligodendrocytes ↓	TNF-α ↓ IL-1β ↓ IL-6 ↓ iNOS ↓ COX-2 ↓ Caspase-3 activation ↓	M1 Activation ↓ MMP-9 ↓ p38MAPK expression ↓ proNGF expression ↓	MAPKs pathway	[57]
GV26 GB34	*Dumain* *Danjing*	MA	Spinal cord injury	Neuropathic pain ↓ Mechanical allodynia ↓ Thermal hyperalgesia ↓	PGE2 ↓	M1 Activation ↓ p38MAPK expression ↓ ERK activation ↓	MAPKs pathway	[58]

Continued to Table 2

Acupoints	Medrian	Type	Model	Efficacy of acupuncture	Effect on inflammation-related factors	Effect on microglia	Signaling pathway	Ref.
PC6 LI11 SP8	*Xinbaojing* *Dachangjing* *Pijing*	EA	MCAO	Neurological scores ↓ Necrosis of hippo-campal neurons ↓	TNF-α ↓ IL-1β ↓ IL-6 ↓ TLR-4 ↓ TRAF6 ↓ IKKβ ↓ NF-κB p65 ↓	M1 Activation ↓	TLR-4/NF-κB pathway	[56]
ST36 SP6	*Weijing* *Pijing*	EA	α-synuclein mutant model	Movement ↑ Loss of dopaminergic neurons ↓ Loss of motor neurons ↓ Astrocytic α-synucle-in expression ↓	TNF-α ↓ IL-1β ↓	M1 Activation ↓ Astrogliosis ↓	Nrf2-ARE pathway	[54]
GB34 LR3	*Danjing* *Ganjing*	MA	PD	DA ↑ Loss of dopaminergic neurodegeneration ↓ Loss of TH immuno-reactivity ↓	COX-2 ↓ iNOS ↓	MAC-1 ↓	NA	[32]
GV20 GB34 LR3 ST36 SP10	*Dumai* *Danjing* *Ganjing* *Weijing* *Pijing*	EA	Limb ischemia-reperfusion	Survival rate ↑ Cognitive function ↑ Neuronal apoptosis ↓ Oxidative damage ↓	SOD ↓ MDA ↓	M1 Activation ↓	NA	[60-61]

When came back to dementia, although few study has been reported on the mechanism of acupuncture on microglia modulation. Still, we found that some acupoints were shared between other CNS disorders and dementia, such as GV20, ST36 [41]. What's more, under the intervention of acupuncture, a bench of pro-inflammation factors (*i.e.*, TNF-α, IL-6, IL-1β, iNOS, COX-2) were significantly reduced in both clinic and *vivo*; in *vivo*, microglia M2 phenotype markers, such as Arg-1 and TGF-β were increased[59].

Therefore, we speculate that the inhibition of M1 microglial activation mediated by TLRs/NF-κB and MAPKs pathways may be one of the key mechanisms of acupuncture regulating neuroinflammatory response and improving cognitive impairment in AD, VD and PD (Figure 2).

3 Conclusion

Acupuncture provides a large range of effects, including the systematic reduction of neuroinflammation, which may improve cognitive ability. The perspective evidence of stimulating the acpoints distributed on head and some distal extremities of body surface may play an important role in treating dementia by inhibiting M1 microglial activation in multiple signal pathways, such as TLRs pathway, MAPKs pathway. However, further studies are still needed to explore the function of signal transductions as well as the reason of specificity of acupuncture in inhibiting microglial activation.

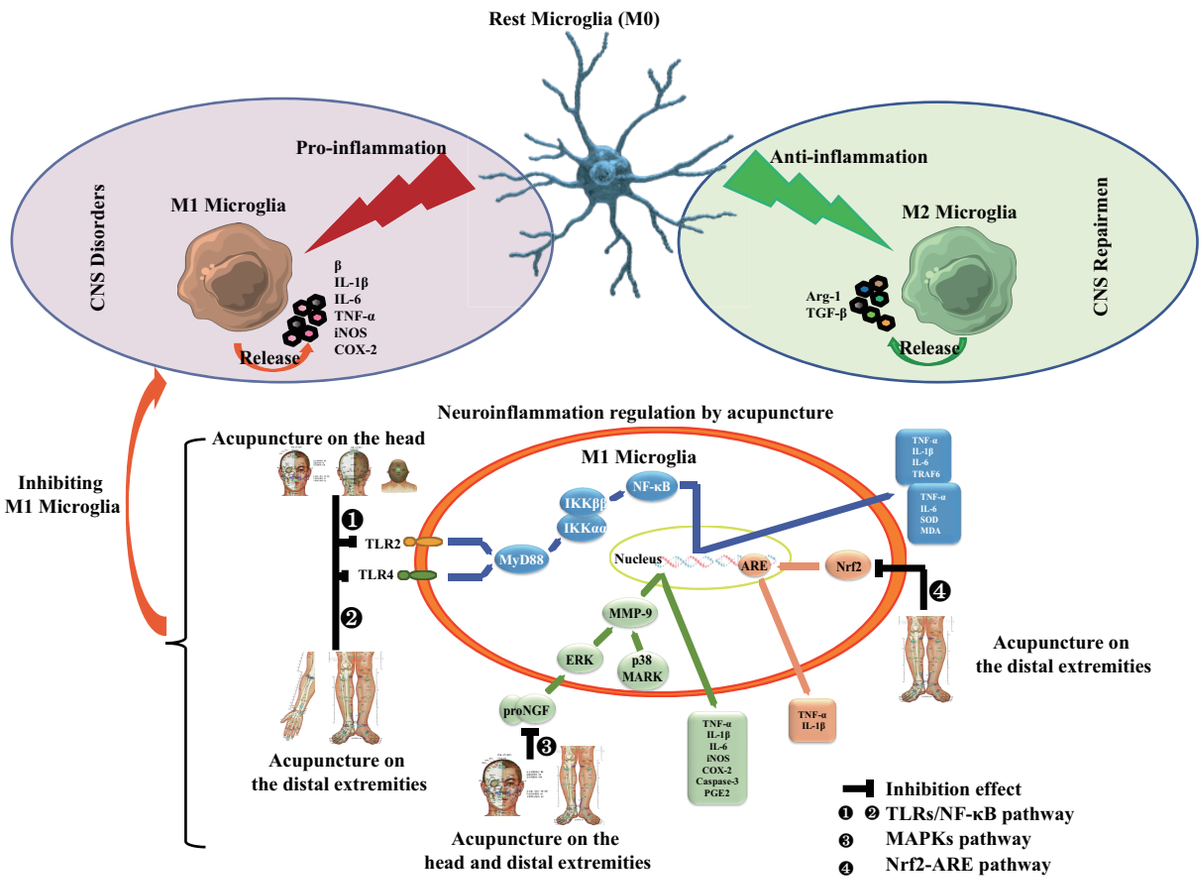

Fig. 2　Acupuncture inhibits M1 Microglia activation——acupoints mainly distributed on the head and the distal extremities

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针刺改善痴呆神经炎症的作用机制探讨——小胶质细胞激活抑制途径*

谭　琰[1)**]　张亚丽[2)]　张佳妮[2)]　白万柱[3)**]

（[1)] 北京中医药大学生命科学学院，北京 100029；
[2)] 北京中医药大学中医学院，北京 100029；[3)] 中国中医科学院针灸研究所，北京 100700）

摘要　针灸是祖国传统医学中古老而又重要的组成部分，作为一种非药物疗法，它在世界范围内已被广泛应用于多种疾病的治疗，并获得了世界卫生组织的推荐. 越来越多的临床和实验证据表明，针刺可以通过调节神经炎症，改善认知. 炎症是多种神经退行性疾病共有的病理反应，如胶质细胞激活、炎症因子的增加与释放. 目前，针灸抗炎领域已积累了大量工作. 为探讨针灸在痴呆中改善神经炎症的作用，本综述以阿尔茨海默症（Alzheimer's disease，AD）、脑血管痴呆（vascular dementia，VD）、帕金森病（Parkinson's disease，PD）为重点，讨论针刺在胶质细胞激活中的作用机制. 研究发现，分布在14条经络上，集中在头部和四肢远端的穴位与胶质细胞激活调节关系密切，针刺可以通过抑制小胶质细胞的激活，改善神经炎症反应. 在AD、VD、PD等脑病中，本文展望，由TLRs/NF-κB、MAPKs等关键通路介导，抑制M1型小胶质细胞激活途径，可能是针刺调节神经炎症反应，改善认知的关键机制之一.

关键词　针灸，痴呆，小胶质细胞，神经炎症
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** 通讯联系人.
谭琰. Tel：010-53912152，E-mail：yantan@bucm.edu.cn，yantan828@163.com
白万柱. Tel：010-64089390，E-mail：wanzhubaisy@hotmail.com
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