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Review

Effects of Acupuncture on Alzheimer's Disease: Evidence from Neuroimaging Studies*

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ABSTRACT As the worldwide population ages, the prevalence of Alzheimer's disease (AD) increases. However, the results of promising medications have been unsatisfactory. Chinese acupuncture has a long history of treating dementia, but lack of evidence from well-designed randomized controlled trials that validate its efficacy and safety, as well as its lack of clear underlying mechanisms, contribute to its limited application in clinical practice. In recent years, brain imaging technologies, such as functional magnetic resonance imaging and positron emission tomography, have been used to assess brain responses to acupuncture in a dynamic, visual, and objective way. These techniques are frequently used to explore neurological mechanisms of responses to acupuncture in AD and provide neuroimaging evidence as well as starting points to elucidate the possible mechanisms. This review summarizes the existing brain imaging evidence that explains the effects of acupuncture for AD and analyzes brain responses to acupuncture at cognitive-related acupoints [Baihui (GV 20), Shenmen (HT 7), Zusanli (ST 36), Neiguan (PC 6), and Taixi (KI 3)] from perspectives of acupoint specificity and acupoint combinations. Key issues and directions to consider in future studies are also put forward. This review should deepen our understanding of how brain imaging studies can be used to explore the underlying mechanisms of acupuncture in AD.

KEYWORDS acupuncture, Alzheimer's disease, brain response, acupoint specificity, neuroimaging

Alzheimer's disease (AD), which is the most common form of dementia, is a neurodegenerative disease with an insidious onset. It is characterized by progressive memory deficits and cognitive decline, a debilitating decline in executive function and spatial awareness, and other neuropsychiatric disorders.[1] The pathological features associated with cognitive dysfunction include intracellular tau aggregates, which are known as neurofibrillary tangles (NFTs), extracellular senile plaques of amyloid-β, and loss of neurons, mainly in the hippocampus and important cortical and subcortical brain regions.[2] Although accumulating evidence substantiates our understanding of AD, the cause and progression of the disease remain unclear. The 2015 World Alzheimer Report estimated that approximately 135 million people will have dementia by 2050.[3] With an aging worldwide population, the incidence of AD will increase and cause an enormous socioeconomic burden.[3] Cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, are recommended for clinical use according to the guidelines of the National Institute for Clinical Excellence.[4] Use of cholinesterase inhibitors is based on evidence suggesting that AD is caused by reduced synthesis of the neurotransmitter acetylcholine.[5] However, cholinesterase inhibitors provide relatively minor relief of symptoms, do not cure the disease, and have high rates of adverse effects.[6-8] At present, no treatment can stop or reverse the progression of AD. Thus, the exploration of effective AD therapies has become a key public health issue.

Acupuncture has been used in clinical practice in China for more than 3,000 years. It is a relatively safe treatment with few side effects.[9] As an important therapeutic method in Chinese medicine (CM), acupuncture has attracted

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growing attention for its complementary and alternative role in safely and effectively alleviating symptoms of some diseases. Recently, it has been shown to be safe and effective in treating several diseases including urinary leakage among women with stress urinary incontinence,[10] chronic severe functional constipation,[11] and migraine.[12] Many famous ancient acupuncture treatises, such as Zhen Jiu Jia Yi Jing (*A-B Classic of Acupuncture and Moxibustion*) and Zhen Jiu Da Cheng (*Great Complete Collection of Acupuncture and Moxibustion*), have recorded clinical applications of acupuncture in treatment of dementia and other neurological disorders. Results from recent systematic reviews and meta-analyses have indicated that acupuncture therapy can safely improve the cognitive function of patients suffering from AD[13,14] and vascular cognitive impairment.[15] However, the mechanisms underlying the effectiveness of acupuncture treatment remain obscure. It is believed that a neuro-endocrine-immune network induces and influences the effects of acupuncture. Furthermore, acupuncture at a single point or combined acupoints achieves regulatory effects on the human body via multiple targets and pathways.[16-18] Thus, the mechanisms of acupuncture are controversial and unclear.

In recent years, functional brain imaging methods, which dynamically detect brain activity, have been used to study the neurological mechanisms of acupuncture effects.[19] These methods provide a scientific and relatively objective approach to elucidate mechanisms underlying the therapeutic effects of acupuncture.[20,21] Among the various functional brain imaging methods, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are used frequently to explore mechanisms of acupuncture and explain the concepts of acupoints and meridians. PET, a minimally invasive diagnostic imaging procedure, is usually used to investigate neural activity by evaluating changes in regional brain blood flow with radioactive tracers, such as O_{16}-H_2O, or cerebral glucose metabolism with ^{18}F-2-fluoro-deoxy-D-glucose (^{18}FDG). PET can detect brain activity *in vivo* at a molecular level.[22] In its most widely used form during the performance of specific cognitive tasks, fMRI infers regional increases in activity based on increases in blood-oxygen-level-dependent (BOLD) contrast and decreases in activity based on decreases in BOLD.[23] More specifically, BOLD signal changes detected by fMRI are thought to represent integrated synaptic activity by measuring changes in blood flow, blood volume, and the blood oxyhemoglobin/deoxyhemoglobin ratio underlying such synaptic activity.[24] fMRI BOLD signals offer advantages as follows: there is no requirement for an exogenous contrast medium; it has high temporal and spatial resolution; and it is widely used to investigate brain responses to acupuncture stimulation and the effects of acupuncture on neural activity. Accumulating neuroimaging studies in humans have shown that acupuncture can modulate a widely distributed brain network in mild cognitive impairment (MCI, a precursor to AD) and AD patients.[25] In this review, we summarize recent neuroimaging studies assessing acupuncture treatment of AD. The aim of this review was to provide a systematic understanding of the effects of acupuncture on AD from the perspectives of neuroimaging research regarding effects of different acupoints and different combined acupoints.

Acupoint Specificity

A related brain area may be activated initially following acupuncture stimulation at a point. Then, the target organs respond to acupuncture stimulation via a neuro-endocrine-humoral regulatory network.[16-18] This regulatory pattern may explain the phenomenon of multiple targets, multiple pathways, and systematic regulation of acupuncture for AD. Acupoint specificity is the focus of meridian research and the basis of studying therapeutic effects and underlying mechanisms of acupuncture.[26,27] Many studies have demonstrated that brain responses to acupuncture stimulation vary with different acupoints.[28-30] Studies exploring vision-related acupoints found that modulation in the vision-related cortex (BA 18/19) was responsive to the specificity of point Guangming (GB 37) when compared with Jiaoxin (KI 8, a nonvision-related point)[31]or a nearby non-acupoint.[32] Acupuncture at vision-related acupoint GB 37 can also activate the occipital cortex as well as the limbic-cerebellar areas and somatosensory cortex.[32] It is commonly accepted that acupuncture at diverse acupoints can have different effects, even on the same disease.[26] Thus, studying brain area responses to various cognitive-related points may optimize acupoint selection and combination and explain the possible mechanisms of acupuncture for AD and MCI from a perspective that differs from previous reviews.[33,34] Typical determination of cognitive acupoints for treating AD is based on the theory of CM meridians as well as etiology and pathogenesis of AD in CM. At present, many studies have investigated cognitive-related acupoints using healthy subjects, MCI patients, or AD patients. Here, we discuss the existing neuroimaging studies of cognitive-related acupoints as follows.

Effects of Different Acupoints

Studies on Acupoint Baihui (GV 20)

Baihui (GV 20), which belongs to the Governor Vessel,

located on the highest place of the head where all the yang meridians converge. "The Shen (Kidney) deficiency and Governor Vessel occlusion as a consequence of qi stagnation and blood stasis" is taken as the major pathogenesis of dementia according to Chinese acupuncture theory. Thus, nourishing Shen-essence and modifying the Governor Vessel should be regarded as a crucial strategy in treatment of senile dementia based on meridian differentiation.[35] In addition, based on Chinese acupuncture theory, acupuncture and moxibustion at GV 20 can regulate qi of the Governor Vessel, clear the mind, lift the spirits, and nourish yang. Data mining analysis also indicates that GV 20 may have better therapeutic effects on vascular dementia.[36] Previous studies have found that acupuncture and moxibustion at GV 20 or GV 20-centered combined acupoints can improve spatial learning and memory ability in AD animal models by enhancing hippocampal synaptic transmission,[37] inhibiting neuroinflammation,[38] promoting recovery of damaged mitochondria,[39] and suppressing neuronal apoptosis via several signaling pathways.[40,41] The brain relies almost exclusively on glucose as its source of energy, and the glucose level is considered an indicator of neuronal function. Numerous studies indicate that the pathogenesis of AD and MCI is directly associated with glucose metabolism disorders.[42,43] Decreased intake of glucose, which may act as a neurodegenerative component of AD, is the direct substrate of cognitive impairment.[42] Animal studies have shown that glucose metabolic activity in AD model rats decreases in the hippocampus, hypothalamus, cortex, etc.[44] Impaired glucose metabolism in the brain of subjects with AD and MCI is a widely recognized early feature of the disease and is positively correlated with severity of symptoms.[42]

Electroacupuncture (EA) at GV 20 can improve spatial learning and memory ability and enhance glucose metabolism in the hippocampus of APP/PS1 mice.[45] A clinical study used fMRI to investigate neural activity or connectivity of higher cognitive functions by measuring regional hemodynamic (ReHo) changes,[46] which are thought to be closely linked to underlying cellular activity.[47] ReHo indicates a temporal similarity between a voxel and its neighboring voxels and reflects the coordinating function of the idiopathic activity of cerebral neurons.[47] EA at GV 20 induced increased ReHo in several regions including the orbital frontal cortex (OFC), middle cingulate cortex (MCC), precentral cortex, and precuneus (preCUN). Decreased ReHo was found in the anterior cingulate cortex (ACC), supplementary motor area, thalamus, putamen, and cerebellum. The OFC is implicated in integrating and modulating neural activation to monitor and control emotional responses,[48] and the ACC and MCC are also associated with emotional and cognitive processing.[49] The preCUN is associated with a wide spectrum of higher-order cognitive processing such as self-processing operations.[50] These results indicate that EA at GV 20 may induce a specific pattern of neural responses. Another resting fMRI study used ReHo and amplitude of low-frequency fluctuation (ALFF) indices to observe activation/deactivation of psychiatric disorder-related cerebral functional regions by EA at Yintang (GV 29, another acupoint belonging to the Governor Vessel) and GV 20.[51]

ALFF can directly demonstrate blood oxygenation levels and reflect idiopathic activity levels of neurons in the voxels according to their energy under the resting state.[52] Results from ReHo and ALFF showed that activations/deactivations were relatively centralised in Brodmann areas, along with the anterior and posterior lobes of the cerebellum. These brain areas involved in emotional control and emotional regulation.[53-55]The cerebellum has long been regarded as essential only for coordination of voluntary motor activity and motor learning,[56] but it is also involved in cognition and emotion and communicates with the cerebral cortex in a topographically organized manner.[57] A study found that the caudate nucleus (5 min after removing the needles), parahippocampal region and hypothalamus (15 min after needle removal), linked to psychiatric diseases such as AD,[58-60] were the key cerebral regions that functionally connect other cerebral regions in an organized network following acupuncture at GV 20. Among the brain areas connected to the caudate nucleus, parahippocampal region and hypothalamus, Brodmann areas were mainly brain network clusters which function in spatial orientation, emotion, cognition, somatic movement and language. These may be mechanisms by which EA at GV 20 affects psychiatric disorders such as AD.

Studies on Acupoint Shenmen (HT 7)

Shenmen (HT 7), the source point of the Xin (Heart) meridian of Hand-Shaoyin, is commonly used to treat palpitations, insomnia, epilepsy, and other neuropsychiatric disorders according to Chinese acupuncture theory. It may improve brain (especially prefrontal) functions, such as memory, attention, vocalization, and projection abilities, and has shown therapeutic effects in treatment of AD.[61,62] A comparison of acupuncture at HT 7 and Yanglao (SI 6, a noncognitive-related acupoint) in healthy young participants[63] showed that acupuncture at HT 7 can activate brain regions associated with cognitive function mainly in the right postcentral gyrus of the frontal lobe and

left inferior frontal gyrus. Reductions in glucose metabolism are found in the hippocampus, bilateral precuneus, and posterior cingulate and are correlated with symptom severity and functional decline in AD patients.[64,65] Needling at HT 7 can also improve memory ability and cerebral glucose metabolic activity of the hippocampus, thalamus, hypothalamus, and frontal/temporal lobes in an AD rat model.[66] Decreased cerebral blood flow (CBF) has been observed in AD patients,[67] and acupuncture treatment may increase CBF.[68] Acupuncture stimulation also increases CBF in rats.[69] Thus, reduced cerebral glucose metabolism might be associated with decreased CBF in AD and might be attenuated by acupuncture. However, the significance of altered glucose metabolism in different brain regions following acupuncture must be clarified further.

Studies on Acupoint Zusanli (ST 36)

According to CM theory, a deficiency of Pi (Spleen) and Wei (Stomach) is the fundamental cause of AD. Zusanli (ST 36) is the sea point of the Wei meridian of Foot-Yangming and plays an essential role in regulating function of the zang-organ Pi and fu-organ Wei. Many clinical trials investigating efficacy of acupuncture and moxibustion on MCI also regard ST 36 as the key acupuncture point.[62,70,71] In an fMRI study investigating differential cerebral responses to acupuncture stimulation at ST 36 versus non-acupuncture points, more pronounced insula and S2 (secondary somatosensory cortex) BOLD activation as well as precuneus deactivation during ST 36 stimulation were observed.[72] In addition, acupuncture at ST 36 can increase ALFF in widespread brain areas including the cerebral cortex (frontal, temporal, parietal, and occipital lobe), brainstem, and cerebellum. The amplitude and extent are higher than those increased by acupuncture at non-acupoint, and ALFF in brain areas of the left temporal pole, superior temporal gyrus, mid-temporal gyrus, uncus, bilateral forepart of the callosal gyrus, right amygdala, and right inferior gyri orbitales was decreased.[73] Feng, et al[74] investigated functional correlations throughout the entire brain following acupuncture at ST 36 in comparison with acupuncture at a nearby non-acupoint. They found that following acupuncture at ST 36, but not acupuncture at non-acupoint, the limbic/paralimbic regions, such as the amygdala, hippocampus, and anterior cingulate gyrus, emerged as network hubs.

However, fMRI trials investigating brain responses to acupuncture at ST 36 were performed in healthy subjects or patients experiencing pain, with no evaluation of neuropsychiatric disorders. In PET studies,[75,76] Lu, et al[15] reported that acupuncture at ST 36 can activate hippocampus, bilateral limbic system (pyriform cortex), bilateral temporal lobe (olfactory cortex), right amygdala, the left orbital cortex, the left infralimbic cortex, the left cerebellum and the left pons in AD rats. It has been generally acknowledged that the lower blood perfusion and glucose hypometabolism in brain regions related to cognition and memory are striking features of AD[77] and may also be one of the main causes of the progressive cognitive deficit in AD.[78] Recently, olfactory dysfunction has been regarded as a common pathological substrate in neurodegenerative diseases such as AD[79] and olfactory impairment may be an important clinical marker and predictor of preclinical AD in older adults at risk.[80] AD patients not only suffer from cognitive impairment, but also behavioral and psychiatric symptoms such as the common symptoms agitation and depression. The orbital cortex is considered as important in the control of emotions. When damaged, this control, especially the inhibition on impulsivity, can be alternated.[81] These results suggest that needling at ST 36 can increase both blood perfusion and glucose metabolism in multiple brain regions related to AD and thus may have a positive influence on cognition of AD.

Studies on Acupoint Neiguan (PC 6)

The Neiguan (PC 6) point is the connecting point of the pericardium meridian of Hand-Jueyin and one of eight meridian-converging acupoints. According to Chinese acupuncture theory, it has a wide disease spectrum including cardiac, gastric, and neuropsychiatric diseases. Many clinical trials have demonstrated its positive effects.[82-84] Very recently, the fractional amplitude of low-frequency fluctuations (fALFF) was used to investigate effects of acupuncture at PC 6 on spontaneous fluctuations in resting-state BOLD fMRI signals in healthy adult subjects. fMRI showed that acupuncture at PC 6 increased fALFF amplitudes within the ACC, occipital fusiform gyrus, posterior cingulate cortex (PCC), and precuneus (PCU). In contrast, during post-acupoint stimulation resting-state scans, fALFF within the PCC was still significantly higher than pre-acupoint stimulation resting-state scans, while the ACC and cerebellum showed decreased fALFF.[85] In an fMRI trial investigating brain responses to acupuncture at PC 6 in normal subjects and AD patients,[86] the researchers observed that both the frontal and temporal lobes were activated by EA at PC 6 in normal subjects. In contrast, the frontal and temporal lobes, cingulate gyrus, and the cerebellum were activated in AD patients with no other brain regions activated. These findings imply that stimulating PC 6 can change the amplitude of intrinsic cortical activity in the brain. Considering the cognitive functions and deficits of

relevant areas in MCI and AD, acupuncture at PC 6 could potentially affect psychiat and neurological disorders.

Studies on Acupoint Taixi (KI 3)

Taixi (KI 3), the source point of the Shen meridian of Foot-Shaoyin, can tonify Shen qi and nourish Shen-essence according to Chinese acupuncture theory. Based on theory of CM, it is believed that "Shen essence deficiency and brain marrow insufficiency" is an important etiological basis of neurodegenerative diseases represented by AD and Parkinson's disease.[87] The method of tonifying Shen qi and essence is often applied in clinical practice to treat AD with acupuncture therapy or a Chinese herbal compound prescription, which also shows beneficial effects for cognitive improvement.[88-90] Acupuncture at KI 3 activates brain regions related to cognition in elderly patients with MCI,[91,92] demonstrating that KI 3 is closely related to cognition. A study investigated effectsof acupuncture at KI 3 on functional connectivity throughout the entire brain in MCI patients compared with healthy controls.[93] The researchers observed abnormal functional connectivity in the temporal regions (hippocampus, thalamus, fusiform gyrus) implicated in memory encoding and retrieval during the resting state in MCI patients, and acupuncture at KI 3 can significantly enhance connectivity among these regions. Another study using resting-state fMRI measured the amplitude of spontaneous activities to investigate effects of acupuncture at KI 3 or a sham acupointon brain regions in MCI patients.[94] Acupuncture at KI 3 could improve neuronal activities of certain cognitive-related regions including the medial frontal gyrus, inferior temporal gyrus, and posterior cingulate, which are components of the default network. The significantly enhanced correlations in memory-related brain regions following acupuncture may be linked to the therapeutic effects of acupuncture for the treatment of MCI.

Based on the existing evidence, we found that acupuncture at different cognitive points can activate different brain response processes. However, overlapping activated brain areas, which include the frontal lobe, limbic system, and cerebellum, are induced by needling at different single cognitive acupoints. It is noteworthy that the different activated brain regions induced by acupuncture at different acupoints are associated with cognitive deficits in AD, which may be the cause of the different effects of acupuncture at a single point. It seems reasonable that activated brain areas differ among these single cognitive acupoints since incorporation of AD or MCI patients during the scanning process could also cause activation of noncognitive-related brain regions.

Effects of Different Combined Acupoints

Most fMRI and PET studies mentioned above focused on cerebral functional imaging with acupuncture at a single point in AD and MCI patients. However, in clinical practice, acupuncture treatment usually involves a combination of acu points based on syndrome differentiation or meridian differentiation. Studies based on fMRI demonstrated that acupuncture at different acupoints or different combined acupoints can activate the corresponding encephalic regions sequentially and specifically.[95] Clinical trials have also demonstrated that the efficacy of combined acupoints and a single acupoint differs in different diseases. A single point was better than multiple points in relieving menstrual pain and preventing pain occurrence.[96] In contrast, stimulation at PC 6 and Hegu (LI 4) was more effective in alleviating postoperative nausea and vomiting than needling only at PC 6.[83]

According to CM theory, Taichong (LR 3), the source point of the Gan (Liver) meridian of Foot-Jueyin, can regulate Gan qi and clear the mind in a wide range of symptoms and diseases including nausea, vomiting, vertigo, tinnitus, irregular menstruation, epilepsy, depression, and other neurological disorders. Hegu (LI 4) point is the source point of the large intestine meridian of Hand-Yangming and is one of the most commonly used acupoints in acupuncture therapy. LR 3-LI 4 points can collectively harmonize yin and yang, regulate qi and blood, and improve cognitive ability of AD patients. Clinical trial also proved that acupuncture at LR 3-LI 4 points can activate certain cognitive-related regions in AD and MCI patients.[97] Most of the regions involved the temporal and frontal lobes, which are closely related to memory and cognition. Using MRI, many studies have demonstrated AD-related hippocampal abnormalities including atrophy,[98] hypometabolism,[99] and decreased activity.[100] Furthermore, several fMRI studies reported markedly reduced functional connectivity in hippocampus-related memory networks in early-stage AD[101] as well as in MCI.[102] One resting-state fMRI study found stronger recovery of hippocampal functional connectivity after donepezil treatment in AD patients,[103] which indicates some plasticity in hippocampal connectivity. Decreased hippocampal connectivity in several frontal and temporal regions were observed in AD patients, and acupuncture at LR 3-LI 4 points can increase connectivity in most of these hippocampus-related regions.[68] These results indicated that acupuncture at LR3-LI4 points combination could be a choice to treat cognition dysfunction.

Another cognitive-related acupoint combination, called Tiaoshen Yizhi (TSYZ) acupoints, has also been shown

to exert therapeutic effects in patients with MCI.[104] This acupoint combination consists of Sishencong (EX-HN 1), Yintang (EX-HN 3), PC 6, KI 3, Fenglong (ST 40), and LR 3, all of which are commonly selected to treat AD patients. Patients with TSYZ treatment exhibited improved cognitive performance after acupuncture. Resting-state fMRI showed that connections between cognition-related regions, such as the insula, dorsolateral prefrontal cortex, hippocampus, thalamus, inferior parietal lobule, and anterior cingulate cortex, increased after acupuncture at TSYZ acupoints. The insula, dorsolateral prefrontal cortex, and hippocampus acted as central brain hubs. These results indicate that acupuncture at these combined acupoints can regulate brain networks by increasing connectivity between cognition-related regions.

Another clinical trial also provided compelling evidence that acupuncture at combined acupoints of HT 7, ST 36, ST 40, and KI 3 has a potential effect on AD.[62] The right main hemisphere (the temporal lobe, such as the hippocampal gyrus and insula, as well as some areas of the parietal lobe) and the left side (the temporal lobe, parietal lobe, and some regions of the cerebellum) were activated. The activated regions induced by combined acupoints were consistent with areas known to be impaired in brains of AD patients and closely correlated with cognitive function.

At present, few studies have investigated brain responses to acupuncture using different acupoint combinations. Although activated cognition-related brain regions were observed following acupuncture using different acupoint combinations as mentioned above, these combined points were not the classical combination based on theory of CM and may yield reduced efficacy compared with the dominant combined acupoints. Thus, these findings must be validated further. Based on syndrome differentiation of CM, the pathogenesis of AD involves Governor Vessel occlusion, deficiency of Shen essence and brain marrow, qi stagnation and blood stasis, so acupoints able to regulate Governor Vessel, qi and blood, supplement Shen essence and brain marrow should be taken into consideration. Since altered gut microbiota was found to be associated with AD,[105] acupuncture at acupoints in abdominal area could have therapeutic effects for AD. A study found that acupuncture at combined acupoints that consisted of Zhongwan (CV 12), Xiawan (CV 10), Qihai (CV 6), Guanyuan (CV 4), Qixue (KI 13), Shangqu (KI 17), and Huaroumen (ST 24) which were all located at abdomen in subjects with an average age of 63 years can enhance intensity of functional connectivity between the bilateral hippocampus (seed points) and other brain areas involved in memory, emotion and cognition.[106] Therefore the "dominant combined acupoints" should deeply correlate with the pathogenesis of AD.

Relationship between Brain Response Induced by Acupuncture and AD Pathogenesis

The existing evidence on brain response of acupuncture for AD were mainly from fMRI and PET studies that validated brain responses by evaluating regional brain blood flow and glucose metabolism changes. So elucidation of the correlation between blood flow, glucose metabolism and AD pathogenesis could explain the possible mechanisms of therapeutic effects of acupuncture on AD. Accumulating evidence suggests that glucose metabolism disorder is associated with AD and AD is also regarded as type 3 diabetes.[107,108] Blood glucose metabolism regulation depends mainly on insulin-based regulation pathway, in which the insulin receptor-mediated signaling pathway plays a key role.[109] PI3K/Akt/GSK-3β signaling pathway is involved in the insulin signaling transduction, and GSK-3β is regulated by insulin in this signaling pathway. Studies have shown that PI3K/Akt/GSK-3β signaling pathway plays a significant role in neuroprotection and enhances cell survival by stimulating cell proliferation, inhibiting neuroinflammation and neuron apoptosis.[108,110] However, dysfunction of this signaling pathway will increase

GSK-3β activity and lead to β-amyloid deposition and hyperphosphorylation of microtubule-associated protein tau,[111,112] and thus impairs synaptic plasticity and cause cognitive impairment.[113,114] Previous reviews have concluded that acupuncture can ameliorate cognitive impairment of AD mouse model by inhibiting Aβ protein deposition and tau hyperphosphorylation, reducing oxidative stress, inhibiting neuronal apoptosis as well as enhancing neurotransmission.[33,34] We speculate that blood glucose metabolism regulation, achieved by acupuncture which could correlate with PI3K/Akt/GSK-3β signaling pathway, could also be one of the possible mechanisms of therapeutic effects of acupuncture for AD (Figure 1, Appendix 1) since cerebral blood flow and cerebral glucose metabolism disorder is associated with neuron mitochondria injury,[115] cerebral amyloid angiopathy,[116] tau pathology,[117] and neuroinflammation.[118] Kim, et al[119] reported that PI3K/Akt signaling pathway may play a central role in acupuncture-induced dopaminergic neuron protection and motor function improvement in a mouse model of Parkinson's disease. Our ongoing studies have also found that EA treatment can ameliorate cognitive deficits in AD rats by inhibiting GSK-3β activity which induces hippocampal neurotransmission enhancement.[37,120] Whether acupuncture

at cognition-related points as reviewed above regulates brain glucose metabolism in AD and MCI via the modulation of PI3K/Akt/GSK-3β signaling pathway needs to be validated.

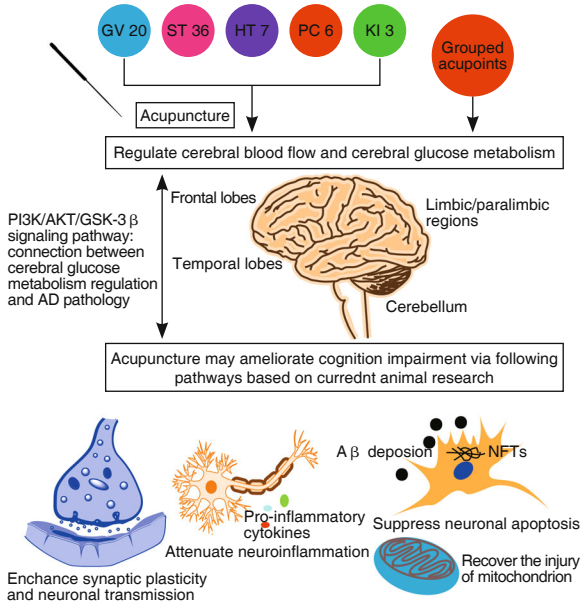

Figure 1. Possible Relationship Between Acupuncture-Induced Brain Response and Pathology of Alzheimer's Disease Based on Existing Evidence

Notes: Current neuroimaging studies validating acupuncture-induced brain responses in AD are based on the evaluation of regional brain blood-oxygen-level-dependent (BOLD) contrast and glucose metabolismchanges, which may involve in PI3K/AKT/GSK-3β signaling pathway. This signaling pathway is also closely related to AD pathologies such as abnormal β-amyloid metabolism, neurofibrillary tangles (NFTs), synaptic plasticity impairment, neuroinflammation, mitochondria injury and neuron apoptosis. Animal studies have shown that acupuncture can ameliorate these pathologies. However, whether PI3K/AKT/GSK-3β signaling pathway is involved in acupuncture-induced protective effects has not been validated yet.

Looking to the Future

fMRI and PET are noninvasive neuroimaging technologies that enable us to study the underlying mechanisms of acupuncture for treatment of AD in a dynamic and objective way. Although accumulating neuroimaging studies have investigated activated brain areas and functional connectivity in AD and in MCI patients treated by acupuncture, some issues remain obscure. These studies are mostly fMRI and PET studies that validated brain responses by evaluating changes in regional brain glucose metabolism and BOLD contrast. However, altered brain metabolism is not the only cause of AD, which also involves epigenetic dysregulation,[121] altered gut microbiota,[105] neuroinflammation,[122] oxidative stress,[123] and dysregulation of lipid metabolism.[124] Thus, brain glucose metabolism and BOLD contrast cannot fully explain the impact of acupuncture on neural activity. Further research should examine the relationship between cerebral metabolic activity and changes in brain regions that define AD pathologically. This may provide a new direction for elucidating the underlying mechanisms of acupuncture for AD. What's more, the methods of manipulation at acupoints need to be considered in future neuroimaging studies since the methods of manipulation play a significant role in therapeutic effects of acupuncture and different manipulation methods may induce different brain responses. However, the existing evidence mainly concentrated on brain response to acupuncture at cognition-related acupoints with comparisons to sham acupuncture but no comparison to the methods of acupuncture manipulation. The impact of frequency of EA on brain response were also less studied. Our previous studies have found that high-frequency EA may yield a stronger protective effect on hippocampal synaptic plasticity and spatial learning and memory abilities compared with low or medium-frequency EA in AD rats.[37,120] Whether high-frequency EA may induce more specific targeted brain response or strengthen the functional connectivity of brain networks associated with memory and cognition remains elucidated. So influence of EA parameters on AD brain response in future neuroimaging studies also needs to be considered.

In conclusion, to some degree, neuroimaging methods suggest that acupoint specificity is a significant factor impacting brain responses.[125-128]However, the synergistic effects of different combined acupoints, which can reinforce[83] or weaken one another,[96] can also activate different brain areas and impact therapeutic effects of acupuncture.[129-131] Thus, additional novel and classical cognitive points or combined acupoints should be selected for future neuroimaging studies to observe differences in activated regions and identify the dominant acupoints and grouped acupoints for treatment of AD. With increased understanding of brain regions involved in the pathology and progression of AD, using neuroimaging technologies to study target brain regions and mechanisms underlying the efficacy of acupuncture and to identify dominant acupoints and combined acupoints for treating AD may improve the therapeutic effects of acupuncture for AD and promote its wider clinical application.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Author Contributions

Yu CC drafted the manuscript, Ma CY helped illustrate the

figure, Wang H contributed to the writing method, Kong LH helped revised the manuscript, Zhao Y contributed to the conception and provided instructions on neuroimaging issues, Shen F and Wu M contributed to the references preparation.

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