

INFORMATION STUDY

Acupoint combinations used for treatment of Alzheimer's disease: A data mining analysis

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Shenmen (HT 7), Zusanli (ST 36), Neiguan (PC 6), Fengchi (GB 20), Taixi (KI 3), Dazhui (GV 14), Shenshu (BL 23), Sanyinjiao (SP 6), Shenting (GV 24), Fenglong (ST 40), Xuanzhong (GB 39), Shuigou (GV 26) and Taichong (LR 3) were of higher frequency in the treatment of AD with acupuncture and moxibustion. Most acupoints were selected from the Governor Vessel. The commonly used acupoints were located on the head, face, neck and lower limbs. The combination of the local acupoints with the distal ones was predominated. The crossing points among the specific points presented the advantage in the treatment. The association analysis indicated that the correlation among Fengchi (GB 20)-Baihui (GV 20) was the strongest, followed by combinations of Dazhui (GV 14)-Baihui (GV 20), Shenshu (BL 23)-Baihui (GV 20) and Neiguan (PC 6)-Baihui (GV 20) and indicated the common rules of the clinical acupoint selection and combination for AD.

CONCLUSION: Our findings provide a reference for acupoints selection and combination for AD in clinical acupuncture practice.

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Keywords: Alzheimer disease; Acupuncture points; Clinical application; Data mining**INTRODUCTION**

Alzheimer's disease (AD), the most prevalent cause of dementia, is characterized as a chronic, progressive neurodegenerative, severe and incurable disorder. AD is associated with memory loss and cognition impairment accompanied by abnormal behavior and changed per-

sonality. The pathological features associated with the cognitive dysfunction are neurofibrillary tangles (NFTs) and senile plaques (SP), combined with neuron loss mainly in the hippocampus and important cortical and subcortical brain regions.¹ It is estimated that nearly 40 million people mostly older than 60 years have dementia worldwide, and this figure is projected to reach over 115 million by 2050, and making it one of the most threat to elderly health and presenting one of the biggest healthcare issues.² Though the situation is severe, there is no effective therapy capable of alleviating symptoms or slowing down disease progression.³

Acupuncture, which is an important therapy method in Chinese medicine, has attracted growing attention for its complementary and alternative role in alleviating symptoms of some diseases safely and effectively. And recently it has been proved safe and effective in several diseases, including urinary leakage among women with stress urinary incontinence,⁴ chronic severe functional constipation,⁵ and migraine.⁶ It has also indicated that acupuncture can ameliorate cognitive impairment and improve memory in AD patients.⁷ Animal studies has found that the therapeutic effects of acupuncture may be achieved *via* multiple pathways, including clearing A β protein deposition,⁸ inhibiting tau protein hyperphosphorylation,⁹ prompting neural transmission,¹⁰ reducing oxidative stress.¹¹ The acupoints selection and combination play a critical role in impacting the therapeutic effects of acupuncture. However, determining the most effective acupoints selection and combination for AD still remains to be elucidated. Insufficient or improper acupoints selection and combination may contribute to a limited clinical therapeutic effects and the application of acupuncture for AD.

In recent years, data mining method has been used to discover potential acupoints and Chinese herbs for improving the therapeutic effects of disease. Clinical trial has demonstrated that the dominant acupoints of Shaoyang Meridian, which was based on the data mining results, were effective in alleviating pain symptoms and reducing migraine recurrence for a long time.⁶ Also, acupuncture on Zusanli (ST 36) of the Stomach Meridian was more effective than acupoints of the Gallbladder Meridian in alleviating functional dyspepsia.¹² These results may provide evidence that data mining method can be a promising and useful method to determine the rules of acupoints selection and combination for treating diseases.

In this data mining analysis, we aimed to discover acupoint combinations that were used to treat AD. Hopefully this can provide evidence-based information for AD treatment with acupuncture.

METHODS

Data searching

Chinese Biomedicine Database ([http://www.sinomed.](http://www.sinomed.ac.cn/)

<http://www.cnki.net/>), China National Knowledge Infrastructure (<http://www.cnki.net/>), Wanfang Database (<http://www.wanfangdata.com.cn/>), and PubMed (<http://www.pubmed.com/>) were searched for published literature on acupuncture therapy for AD from January 1978 to August 2017. Search strings for PubMed were as follows:

1#"acupuncture"or "electroacupuncture" or "hand acupuncture"or"moxibustion" or "acupoint";

2# "Alzheimer's disease" or "Alzheimer's"or "AD"or "dementia";

3# 1#AND 2#.

Literature published from January 1978 to August 2017 on acupuncture and moxibustion therapy for AD were included. Language was restricted to Chinese and English.

Review process

Inclusion criteria and exclusion criteria of literature for data mining were evaluated according to the following items.

Types of studies

Inclusion criteria: all clinical trials evaluating the effect of acupuncture and/or moxibustion, with or without methods of randomization and/or control were included. Since the present data mining analysis was aimed at investigating the rules of effective acupoints selection and combination, only trials that proved the therapeutic efficacy of acupuncture and/or moxibustion for AD were included, studies with no significantly dominant efficacy in acupuncture and/or moxibustion group compared to control groups were not included.

Exclusion criteria: case reports, experts' experience, reviews, animal studies, systematic reviews, and meta-analysis were excluded.

Types of participants

Inclusion criteria: clinical trials involving participants diagnosed with AD were included.

Exclusion criteria: trials evaluating the therapeutic effect of acupuncture for cognitive impairment caused by other factors (e.g., vascular dementia, dementia with Lewy bodies, frontotemporal dementia, or other mental and emotional disorders (such as schizophrenia and depression) were excluded.

Types of intervention

Inclusion criteria: the treatments for AD had to involve needle insertion and/or moxibustion at either traditional meridian acupoints or extraordinary acupoints. Acupuncture and/or moxibustion were either used alone or in addition to other interventions (e.g., Chinese herbs, western drug, diet, music and exercise therapy). Trials investigating and/or comparing different acupoints prescriptions or different manipulation methods of acupuncture or moxibustion for AD were also included.

Exclusion criteria: trials investigating the modern methods of stimulating acupoints without needle insertion

(e.g., laser stimulation or transcutaneous electrical stimulation) were excluded. Trials of microacupuncture systems were also excluded, since the theory of microacupuncture is not related to traditional acupoints. Trials evaluating stimulating trigger points for AD were excluded since the theory of trigger points is not related to traditional Chinese acupuncture theory.

Data collection

Two reviewers independently screened the records retrieved from the literature searches. Information about titles, interventions, and main acupoints was extracted using the self-established Excel sheets. Acupoint prescriptions in treatment group but not control group were extracted for data mining. If the studies involved in comparison of therapeutic effects of different acupoint prescriptions, then the most effective acupoint prescription was extracted. All potentially relevant articles were investigated as full text in English or Chinese. Any discrepancies were resolved by consensus or consultation with another reviewer (Kong Lihong). The final version was included and used in case of duplicate publications.

Data extraction

The frequencies of acupoints, meridians, acupoints distribution on different body parts and acupoints attribute were extracted and analyzed.

Description about acupoints and meridians were standardized according to the WHO Standard Acupuncture Point Locations in the Western Pacific Region.¹³

Data processing

Information about acupoints selection and combination can be obtained *via* calculating the acupoints frequency, support degree, confidence and lift based on the data mining algorithm.¹⁴ Support degree is an index to measure the probability that events X and Y occur simultaneously under specific conditions. The algorithm is as follow: $\text{Support}(X \rightarrow Y) = P(X, Y) / P(I) = P(X \cap Y) / P(I) = \text{num}(X \cap Y) / \text{num}(I)$. I represents the entire dataset, "num()" represents the frequency or times of specific or defined dataset. Support degree is used to measure the statistical significance of association rules. Confidence is an index to measure the probability that the event Y occurs under the condition that event X prior occurs. The algorithm is as follow: $\text{Confidence}(X \rightarrow Y) = P(Y|X) = P(X, Y) / P(X) = P(X \cap Y) / P(X)$. Lift displays the ratio of confidence for the rule to the prior probability of having the consequent. The algorithm is as follow: $\text{Lift}(X \rightarrow Y) = P(Y|X) / P(Y)$. In general, association rules are only useful when the support degree and confidence level meet the minimum requirements.

RESULTS

Study selection

Our initial search identified and screened 1923 articles.

Four hundred duplicates were removed. A total of 1432 articles were excluded based on the exclusion criteria. The remaining 91 records were retrieved for more detailed evaluation and 91 acupoints prescriptions were included in our data mining analysis. The selection process is available in Figure 1.

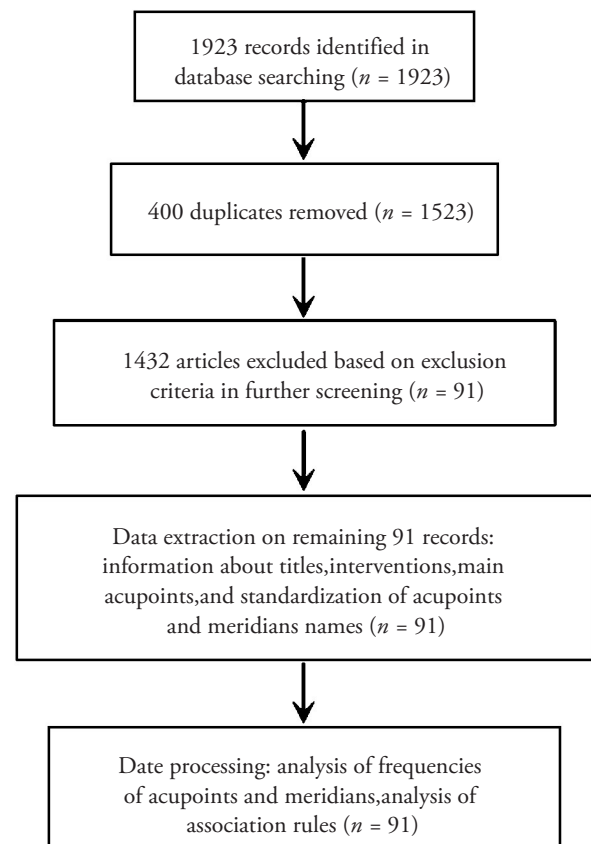


Figure 1 Flow diagram of data mining process

Descriptive analysis

Analysis of acupoints frequency: acupoints frequency was analyzed based on the acquired 91 acupoint prescriptions. Sixty acupoints were involved in the treatment of AD among which there were 58 meridian-acupoints and 2 extraordinary acupoints and they were recorded for total 508 times in modern clinical literature regarding acupuncture and moxibustion for AD. The top 15 acupoints used frequently were Baihui (GV 20), Sishencong (EX-HN 1), Shenmen (HT 7), Zusanli (ST 36), Neiguan (PC 6), Fengchi (GB 20), Taixi (KI 3), Dazhui (GV 14), Shenshu (BL 23), Sanyinjiao (SP 6), Shenting (GV 24), Fenglong (ST 40), Xuanzhong (GB 39), Shuigou (GV 26) and Taichong (LR 3) in turn. Detailed information can be checked in Figure 2A.

Analysis of meridian frequency: there were 58 meridian-acupoints which were recorded 458 times in the 91 acupoint prescriptions. Their distribution of meridian can be checked in Table 1 and Figure 2 B. Thirteen meridians were involved. The most frequently used meridian was the Governor Meridian (134 times) followed by the Stomach Meridian of Foot Yangming (50 times), the Gallbladder Meridian of Foot Shaoyang (49 times) and Bladder Meridian of Foot Taiyang (41

times) which accounted for 55.91% together of total frequencies up to 284 records. Thirty-four acupoints belonged to the 4 meridians which accounted for 56.67% of total acupoints number.

What should be noted that *Yang* meridians were used more frequently (58.68%) compared with *Yin* meridians (32.48%). The distribution pattern of acupoints also indicated that inharmony of *Qi* and blood of these meridians may contribute to the pathogenesis of Alzheimer's dementia based on Chinese acupuncture theory. These results implied that acupoints belonging to the Governor Meridian, Stomach Meridian of Foot Yangming and Bladder Meridian of Foot Taiyang could be taken much into consideration in selecting acupoints for treating dementia.

Analysis of frequency of acupoints on different body parts: acupoints on the head, face, and neck were used most frequently with a total number of 23 acupoints and a total frequency of 218 times, followed by acupoints on the lower limbs (133 times), upper limbs (81 times), back and lumbar (34 times) and chest and abdomen (32 times). These findings indicated that acu-

points in head, face, and neck were selected more frequently in AD treatment, which were in accordance with the basic principle of acupoint selection, namely "local lesion can be treated by vicinal acupoints". Detailed information can be checked in Table 2 and Figure 2C.

Analysis of frequency of special acupoints: special acupoints refer to meridian-acupoints which has unique name and special or oriented therapeutic effects. Special acupoints are used widely and play a vital role in the theory of Chinese acupuncture and clinical application. According to our data mining results, the main acupoints involved in the treatment of AD included special acupoints and non-special acupoints with specific points being dominant. Convergent acupoints, five-shu acupoints, yuan-source acupoints and luo-connecting acupoints were of high frequency. The top 3 convergent acupoints were Baihui (GV 20), Fengchi (GB 20), Dazhui (GV 14). The top 3 five-shu acupoints were Shenmen (HT 7), Zusanli (ST 36), Taixi (KI 3). The top 3 yuan-source acupoints were Shenmen (HT 7), Taixi (KI 3), Taichong (LR 3). The top 3

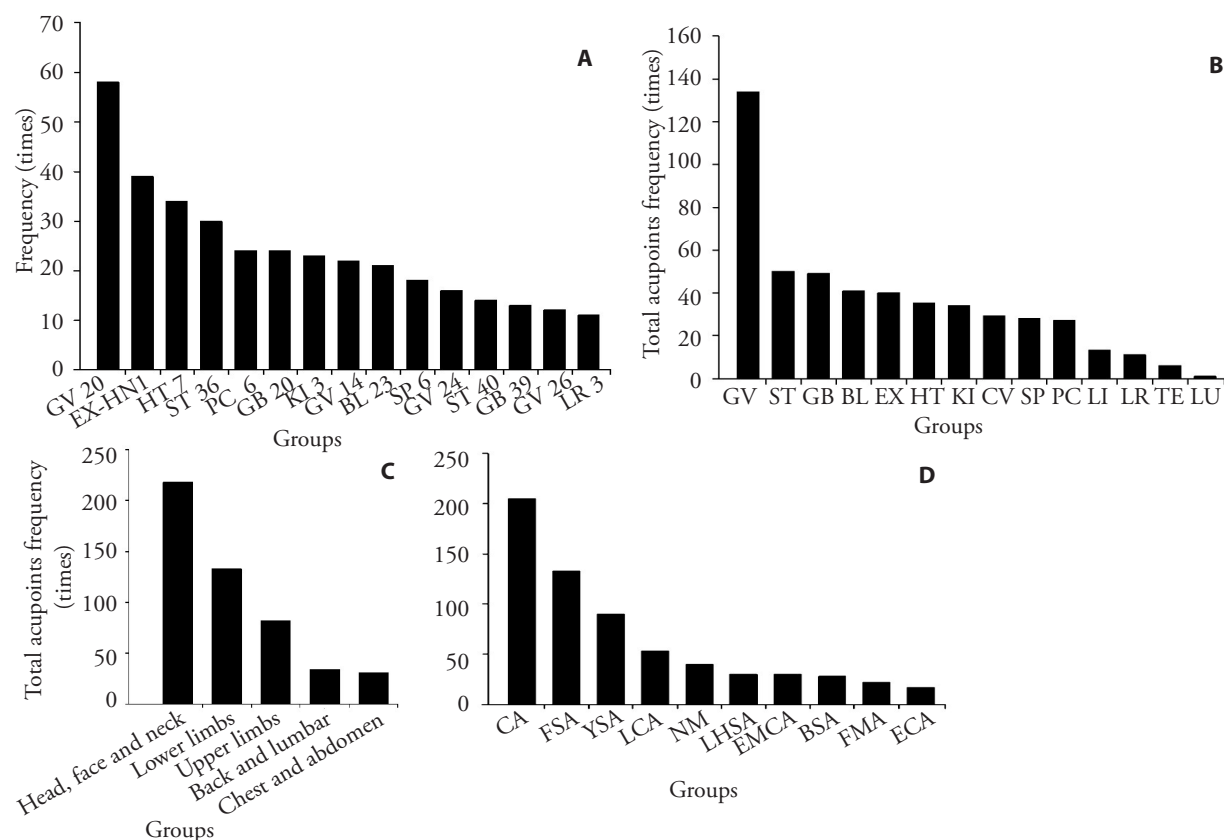


Figure 2 Frequencies of acupoints in different meridians, different body parts and different types for AD
 A: top 15 acupoints used frequently in AD; B: the meridians distribution associated with AD; C: the body parts distribution of acupoints in the treatment of AD; D: the types and attribute of acupoints for AD. GV 20: Baihui (GV 20); EX-HN 1: Sishencong (EX-HN 1); HT 7: Shenmen (HT 7); ST 36: Zusanli (ST 36); PC 6: Neiguan (PC 6); GB 20: Fengchi (GB 20); KI 3: Taixi (KI 3); GV 14: Dazhui (GV 14); BL 23: Shenshu (BL 23); SP 6: Sanyinjiao (SP 6); GV 24: Shenting (GV 24); ST 40: Fenglong (ST 40); GB 39: Xuanzhong (GB 39); GV 26: Shuigou (GV 26); LR 3: Taichong (LR 3). AD: Alzheimer's disease; GV: Governor Vessel; GB: Gallbladder Meridian of Foot Shaoyang; ST: Stomach Meridian of Foot Yangming; BL: Bladder Meridian of Foot Taiyang; EX-HN: extraordinary acupoint; HT: Heart Meridian of Hand Shaoyin; KI: Kidney Meridian of Foot Shaoyin; CV: Conception Vessel; SP: Spleen Meridian of Foot Taiyin; PC: Pericardium Meridian of Hand Jueyin; LI: Large Intestine Meridian of Hand Yangming; LR: Liver Meridian of Foot Jueyin; TE: Triple Energizer of Hand Shaoyang; LU: Lung Meridian of Hand Taiyin. CA: Convergent acupoint; FSA: Five-Shu acupoint; YSA: Yuan-source acupoint; LCA: Luo-Connecting acupoint; NMA: Non-meridian acupoint; FMA: Front-Mu acupoint; LHSA: Lower He-Sea acupoint; EMCA: Eight meridian-converging acupoints; BSA: Back-Shu acupoint; ECA: eight confluent acupoint.

Table 1 Frequency and percentage of acupoints used for Alzheimer's disease in literature

Meridians	Frequency	Percentage (%)	Acupoints number	Acupoints (frequency)
GV	134	26.38	12	Baihui (GV 20) (58), Dazhui (GV 14) (22), Shenting (GV 24) (16), Shuigou (GV 26) (12), Yintang (GV 29) (6), Fengfu (GV 16) (5), Shangxing (GV 23) (4), Naohu (GV 17) (4), Yamen (GV 15) (3), Qiangjian (GV 18) (2), Mingmen (GV 4) (1), Qianding (GV 21) (1)
ST	50	9.84	7	Zusanli (ST 36) (30), Fenglong (ST 40) (14), Touwei (ST 8) (2), Tianshu (ST 25) (1), Wailing (ST 26) (1), Renying (ST 9) (1), Huaroumen (ST 24) (1)
GB	49	9.65	7	Fengchi (GB 20) (24), Xuanzhong (GB 39) (13), Benshen (GB 13) (7), Wangu (GB 12) (2), Xuanli (GB 6) (1), Qubin (GB 7) (1), Shuaigu (GB 8) (1)
BL	41	8.07	8	Shenshu (BL 23) (21), Ganshu (BL 18) (5), Tianzhu (BL 10) (5), Geshu (BL 17) (4), Feiyang (BL 58) (3), Guanyuanshu (BL 26) (1), Jueyinshu (BL 14) (1), Xinshu (BL 15) (1)
EX	40	7.87	2	Sishencong (EX-HN 1) (39), Jiaji (EX-B 2) (1)
HT	35	6.89	2	Shenmen (HT 7) (34), Shaochong (HT 9) (1)
KI	34	6.69	3	Taixi (KI 3) (23), Dazhong (KI 4) (6), Yongquan (KI 1) (5)
CV	29	5.71	6	Danzhong (CV 17) (8), Guanyuan (CV 4) (8), Qihai (CV 6) (6), Zhongwan (CV 12) (5), Shangwan (CV 13) (1), Xiawan (CV 10) (1)
SP	28	5.51	3	Sanyinjiao (SP 6) (18), Xuehai (SP 10) (7), Taibai (SP 3) (3)
PC	27	5.31	4	Neiguan (PC 6) (24), Daling (PC 7) (1), Zhongchong (PC 9) (1), Jianshi (PC 5) (1)
LI	13	2.56	3	Hegu (LI 4) (8), Quchi (LI 11) (4), Yingxiang (LI 20) (11)
LR	11	2.17	1	Taichong (LR 3) (11)
TE	6	1.18	1	Waiguan (TE 5) (6)
LU	1	0.20	1	Shaoshang (LU 11) (1)

Notes: GV: Governor Vessel; GB: Gallbladder Meridian of Foot Shaoyang; ST: Stomach Meridian of Foot Yangming; BL: Bladder Meridian of Foot Taiyang; EX-HN: extraordinary acupoint; HT: Heart Meridian of Hand Shaoyin; KI: Kidney Meridian of Foot Shaoyin; CV: Conception Vessel; SP: Spleen Meridian of Foot Taiyin; PC: Pericardium Meridian of Hand Jueyin; LI: Large Intestine Meridian of Hand Yangming; LR: Liver Meridian of Foot Jueyin; TE: Triple Energizer of Hand Shaoyang; LU: Lung Meridian of Hand Taiyin. Frequencies of meridians refer to the total frequencies of acupoints on the same meridian. The number of acupoints refers to the total number of acupoints on the same.

Table 2 Frequency and percentage of acupoints in different body parts

Distribution	Frequency	Percentage (%)	Acupoints number	Acupoint (frequency)
Head, face, and neck	218	43.76	23	Baihui (GV 20) (58), Sishencong (EX-HN 1) (39), Fengchi (GB 20) (24), Dazhui (GV 14) (22), Shenting (GV 24) (16), Shuigou (GV 26) (12), Benshen (GB 13) (7), Yintang (GV 29) (6), Fengfu (GV 16) (5), Tianzhu (BL 10) (5), Shangxing (GV 23) (4), Naohu (GV 17) (4), Yamen (GV 15) (3), Touwei (ST 8) (2), Wangu (GB 12) (2), Qiangjian (GV 18) (2), Xuanli (GB 6) (1), Qubin (GB 7) (1), Shuaigu (GB 8) (1), Yingxiang (LI 20) (1), Jiaji (EX-B 2) (1), Renying (ST 9) (1), Qianding (GV 21) (1)
Lower limbs	133	26.71	11	Zusanli (ST 36) (30), Taixi (KI 3) (23), Sanyinjiao (SP 6) (18), Fenglong (ST 40) (14), Xuanzhong (GB 39) (13), Taichong (LR 3) (11), Xuehai (SP 10) (7), Dazhong (KI 4) (6), Yongquan (KI 1) (5), Feiyang (BL 58) (3), Taibai (SP 3) (3)
Upper limbs	81	16.27	10	Shenmen (HT 7) (34), Neiguan (PC 6) (24), Hegu (LI 4) (8), Waiguan (TE 5) (6), Quchi (LI 11) (4), Daling (PC 7) (1), Shaoshang (LU 11) (1), Zhongchong (PC 9) (1), Shaochong (HT 9) (1), Jianshi (PC 5) (1)
Back and lumbar	34	6.83	7	Shenshu (BL 23) (21), Ganshu (BL 18) (5), Geshu (BL 17) (4), Mingmen (GV 4) (1), Guanyuanshu (BL 26) (1), Jueyinshu (BL 14) (1), Xinshu (BL 15) (1)
Chest and abdomen	32	6.43	9	Danzhong (CV 17) (8), Guanyuan (CV 4) (8), Qihai (CV 6) (6), Zhongwan (CV 12) (5), Xiawan (CV 10) (1), Tianshu (ST 25) (1), Huaroumen (ST 24) (1), Shangwan (CV 13) (1), Wailing (ST 26) (1)

Notes: GV: Governor Vessel; EX-HN: extraordinary acupoint; GB: Gallbladder Meridian of Foot Shaoyang; BL: Bladder Meridian of Foot Taiyang; ST: Stomach Meridian of Foot Yangming; LI: Large Intestine Meridian of Hand Yangming; KI: Kidney Meridian of Foot Shaoyin; SP: Spleen Meridian of Foot Taiyin; LR: Liver Meridian of Foot Jueyin; HT: Heart Meridian of Hand Shaoyin; PC: Pericardium Meridian of Hand Jueyin; TE: Triple Energizer of Hand Shaoyang; LU: Lung Meridian of Hand Taiyin; CV: Conception Vessel.

luo-connecting acupoints were Neiguan (PC 6), Fenglong (ST 40), Waiguan (TE 5). And Sishencong (EX-HN 1) were the main non-meridian acupoint used for AD. Detailed information can be checked in Table 3 and Figure 2D.

Identification of the combinations: SPSS clementine 12.0 software (IBM, Armonk, NY, USA) was used to conduct the analysis of the top 15 acupoints used frequently, and we set the minimum requirements that support degree $\geq 12\%$ and confidence $\geq 80\%$ (Table 4). The combined acupoints used frequently were obtained, as indicated by the support degree and confidence level meeting the minimum requirements. Results from association analysis indicated that acupoints Baihui (GV 20), Neiguan (PC 6) and Sishencong (EX-HN 1) were more frequently combined or grouped with other dementia-related acupoints. The visual network structures of the 60 acupoints can be checked in Figure 3A and Figure 3B.

DISCUSSION

We performed data mining analysis to identify acupoint combinations that are commonly used for AD. In our study, we found that the acupoint Baihui (GV 20) was of highest frequency. Also, Baihui (GV 20) was strongly associated with other acupoints and combined acupoints, indicating that Baihui (GV 20) was the key acupoint in treating AD with acupuncture and moxibustion. This finding discovering the acupoint

Baihui (GV 20) with potential treating AD also was in accordance with the knowledge of AD based on Chinese acupuncture theory. Baihui (GV 20), which belongs to the Governor Vessel, is located at the point 7 cun directly above the posterior hairline and 5 cun behind the anterior hairline according to the Chinese acupuncture theory. Because of the specific location of Baihui (GV 20) (which is located on the highest place of the head where all the *Yang* meridians converge), acupuncture and moxibustion at Baihui (GV 20) can regulate *Qi* of Governor Vessel, clear the mind, lift the spirits, nourish *Yang* based on Chinese acupuncture theory. Thus, the acupoint Baihui (GV 20) is specifically applied to treating neurological and psychiatric diseases. The kidney deficiency and Governor Vessel occlusion by blood stasis are taken as the major pathogeneses of senile dementia based on Chinese medicine theory, so the acupoints Shenshu (BL 23) and Baihui (GV 20) were chosen in our previous studies to nourish kidney-essence and modify Governor Vessel. In our previous studies, we found that electroacupuncture and moxibustion at Baihui (GV 20)-Shenshu (BL 23) can attenuate cognitive impairment *via* ameliorating the hippocampal synapse loss,²² upregulating the expression of synaptic markers PSD-95 and synaptophysin,²³ enhancing hippocampal synaptic transmission,²⁴ inhibiting neuroinflammation,²⁵ recovering the injury of mitochondria²⁶ and attenuating tau hyperphosphorylation.⁹ Also, EA at Baihui (GV 20)- Shenshu (BL 23) can rescue the function of mitochondria by suppressing the overexpression

Table 3 Frequency of different acupoints

Acupoints attribute	Frequency	Acupoints number	Acupoints (frequency)
CA	195	19	Baihui (GV 20) (58), Fengchi (GB 20) (24), Dazhui (GV 14) (22), Sanyinjiao (SP 6) (18), Shenting (GV 24) (16), Shuigou (GV 26) (12), Danzhong (CV 17) (8), Guanyuan (CV 4) (8), Benshen (GB 13) (7), Fengfu (GV 16) (5), Zhongwan (CV 12) (5), Yamen (GV 15) (3), Touwei (ST 8) (2), Wangu (GB 12) (2), Mingmen (GV 4) (1), Qubin (GB 7) (1), Shuaigu (GB 8) (1), Yingxiang (LI 20) (1), Xiawan (CV 10) (1)
FSA	133	13	Shenmen (HT 7) (34), Zusanli (ST 36) (30), Taixi (KI 3) (23), Taichong (LR 3) (21), Hegu (LI 4) (8), Yongquan (KI 1) (5), Quchi (LI 11) (4), Taibai (SP 3) (3), Daling (PC 7) (1), Shaoshang (LU 11) (1), Zhongchong (PC 9) (1), Shaochong (HT 9) (1), Jianshi (PC 5) (1)
YSA	90	6	Shenmen (HT 7) (34), Taixi (KI 3) (23), Taichong (LR 3) (21), Hegu (LI 4) (8), Taibai (SP 3) (3), Daling (PC 7) (1)
LCA	53	5	Neiguan (PC 6) (24), Fenglong (ST 40) (14), Waiguan (TE 5) (6), Dazhong (KI 4) (6), Feiyang (BL 58) (3)
NMA	40	2	Sishencong (EX-HN 1) (39), Jiaji (EX-B 2) (1)
LHSA	30	1	Zusanli (ST 36) (30)
EMCA	30	2	Neiguan (PC 6) (24), Waiguan (TE 5) (6)
BSA	28	4	Shenshu (BL 23) (21), Ganshu (BL 18) (5), Jueyinshu (BL 14) (1), Xinshu (BL 15) (1)
FMA	22	4	Danzhong (CV 17) (8), Guanyuan (CV 4) (8), Zhongwan (CV 12) (5), Tianshu (ST 25) (1)
ECA	17	2	Xuanzhong (GB 39) (13), Geshu (BL 17) (4)

Notes: GV: Governor Vessel; GB: Gallbladder Meridian of Foot Shaoyang; SP: Spleen Meridian of Foot Taiyin; CV: Conception Vessel; ST: Stomach Meridian of Foot Yangming; LI: Large Intestine Meridian of Hand Yangming; HT: Heart Meridian of Hand Shaoyin; KI: Kidney Meridian of Foot Shaoyin; LR: Liver Meridian of Foot Jueyin; PC: Pericardium Meridian of Hand Jueyin; LU: Lung Meridian of Hand Taiyin; TE: Triple Energizer of Hand Shaoyang; EX-HN: Extraordinary Acupoint; BL: Bladder Meridian of Foot Taiyang.

Table 4 Most frequently used 15 acupoints for Alzheimer's disease

Antecedent	Consequent	Confidence (%)	Support (%)	Lift
Baihui (GV 20)-Sanyinjiao (SP 6)	Neiguan (PC 6)	100.00	13.19	3.79
Shenmen (HT 7)-Sanyinjiao (SP 6)	Neiguan (PC 6)	84.62	12.09	3.21
Baihui (GV 20)- Zusanli (ST36)	Sishencong (EX-HN 1)	86.67	14.29	2.02
Shenting (GV 24)	Sishencong (EX-HN 1)	81.25	14.29	1.9
Sishencong (EX-HN 1)-Neiguan (PC 6)	Baihui (GV 20)	100.00	14.29	1.57
Fengchi (GB 20)- Taixi (KI 3)	Baihui (GV 20)	100.00	12.09	1.57
Fengchi (GB 20)	Baihui (GV 20)	91.67	24.18	1.44
Fengchi (GB 20)-Mingmen (GV 4)	Baihui (GV 20)	91.67	12.09	1.44
Mingmen (GV 4)	Baihui (GV 20)	90.91	21.98	1.43
Sishencong (EX-HN 1)-Fengchi (GB 20)	Baihui (GV 20)	85.71	13.19	1.34
Neiguan (PC 6)-Sanyinjiao (SP 6)	Baihui (GV 20)	85.71	13.19	1.34
Shenshu (BL 23)	Baihui (GV 20)	85.00	21.98	1.33
Neiguan (PC 6)	Baihui (GV 20)	83.33	21.98	1.31
Sishencong (EX-HN 1)-ST36	Baihui (GV 20)	81.25	14.29	1.27
Shenmen (HT 7)-Neiguan (PC 6)	Baihui (GV 20)	80.00	13.19	1.26

Notes: GV: Governor Vessel; SP: Spleen Meridian of Foot Taiyin; HT: Heart Meridian of Hand Shaoyin; ST: Stomach Meridian of Foot Yangming; EX-HN: extraordinary acupoint; PC: Pericardium Meridian of Hand Jueyin; GB: Gallbladder Meridian of Foot Shaoyang; KI: Kidney Meridian of Foot Shaoyin; BL: Bladder Meridian of Foot Taiyang.

of A β -binding alcohol dehydrogenase, increasing the activity of cytochrome oxidase IV and silent information regulator 1 level in hippocampal neuron mitochondria.²⁷ Guo *et al* has also reported that EA at Baihui (GV 20)- Shenshu (BL 23) can reduce neuronal apoptosis, enhance degradation of A, and improve learning and memory recovery in a rat model of AD by upregulating the autophagy pathway²⁸ and suppressing neuronal apoptosis *via* downregulation of notch signaling pathway.²⁹ When acupuncturing at other Baihui (GV 20)-centered acupoint combinations, improvements of spatial learning and memory ability were also observed. For example, EA at Baihui (GV 20)-Shuigou (GV 26) (which also belongs to Du meridian) can improve the spatial learning and memory ability *via* enhancing glucose metabolism in hippocampus in APP/PS1 transgenic mice.³⁰ EA at Baihui (GV 20), Dazhui (GV 14), Shenshu (BL 23) and KI3 can improve mitochondrial function by increasing the activity of hippocampal mitochondria respiratory chain enzyme complexes and ATP concentration.³¹ These findings provide evidence that acupuncturing at combined-acupoints centered on Baihui (GV 20) can ameliorate cognitive impairment of AD *via* multi-targets and multi-pathways.

However, our data mining results should be interpreted with caution due to the following limitations. First, other factors such as the manipulation method of acupuncture, electroacupuncture parameters, amount of stimulation, intervention time and treatment course which can also indirectly influence the therapeutic effects of acupuncture for AD were not mined and ana-

lyzed. Second, only main acupoints were included in our study, adjunct points prescribed based on syndrome differentiation for other symptoms were not included since selection acupoints based on syndrome differentiation is also one of important and general principle of acupoint selection. These can be further mined to discover a more relatively standard guideline. In the future, based on data mining results and previous evidence from experimental studies, determining the specifically activated brain regions in AD induced by acupuncture and moxibustion at dominant and superior single acupoint or combined-acupoints, and furthermore studying and exploring the neuronal circuits changes in activated brain regions could be an important direction of revealing the possible mechanisms of the efficacy of acupuncture and moxibustion for AD.

REFERENCES

- 1 Hane FT, Lee BY, Leonenko Z. Recent progress in alzheimer's disease research, part 1: pathology. *J Alzheimers Dis* 2017; 57(1): 1-28.
- 2 Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: A systematic review and Meta analysis. *Alzheimers Dement* 2013; 9(1): 63-75.e62.
- 3 Folch J, Petrov D, Ettcheto M, et al. Current research therapeutic strategies for alzheimer's disease treatment. *Neural Plast* 2016; 2016: 8501693.
- 4 Liu Z, Liu Y, Xu H, et al. Effect of electroacupuncture on urinary leakage among women with stress urinary incontinence: A randomized clinical trial. *JAMA* 2017; 317(24): 2493-2501.
- 5 Liu Z, Yan S, Wu J, et al. Acupuncture for chronic severe

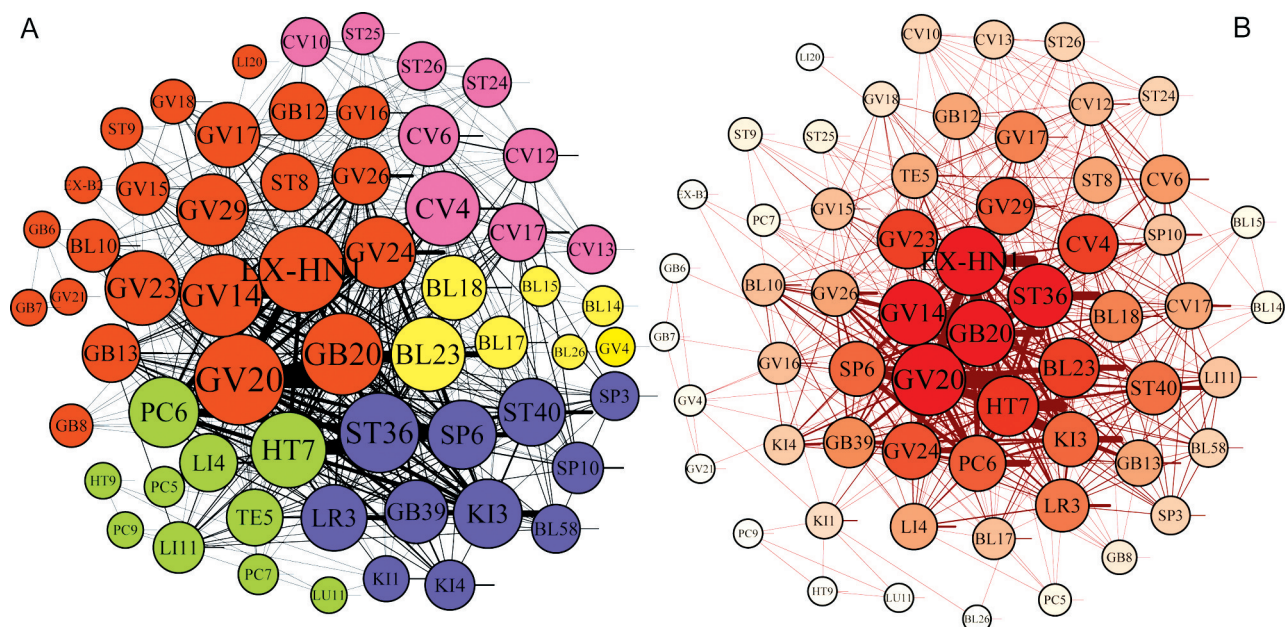


Figure 3 Network structure of acupoints for the treatment of AD

A: distribution of acupoints for AD. Red nodes are acupoints in head, face, and neck; rose red are acupoints in chest and abdomen; yellow nodes are acupoints in back and lumbar; purple nodes are acupoints in lower limbs; green nodes are acupoints in upper limbs; B: visual network structure of the association rules of acupoints. GV 20: Baihui (GV 20); EX-HN1: Sishencong (EX-HN 1); GB 20: Fengchi (GB 20); GV 14: Dazhui (GV 14); GV 24: Shenting (GV 24); GV 26: Shuigou (GV 26); GB 13: Benshen (GB 13); GV 29: Yintang (GV 29); GV 16: Fengfu (GV 16); BL 10: Tianzhu (BL 10); GV 23: Shangxing (GV 23); GV 17: Naohu (GV 17); GV 15: Yamen (GV 15); ST 8: Touwei (ST 8); GB 12: Wangu (GB 12); GV 18: Qiangjian (GV 18); GB 6: Xuanli (GB 6); GB 7: Qubin (GB 7); GB 8: Shuaigu (GB 8); LI 20: Yingxiang (LI 20); EX-B2: Jiaji (EX-B 2); ST 9: Renying (ST 9); GV 21: Qianding (GV 21); CV 17: Danzhong (CV 17); CV 4: Guanyuan (CV 4); CV 6: Qihai (CV 6); CV 12: Zhongwan (CV 12); CV 10: Xiawan (CV 10); ST 25: Tianshu (ST 25); ST 24: Huaroumen (ST 24); CV 13: Shangwan (CV 13); ST 26: Wailing (ST 26); BL 23: Shenshu (BL 23); BL 18: Ganshu (BL 18); BL 17: Geshu (BL 17); GV 4: Mingmen (GV 4); BL 26: Guanyuanshu (BL 26); BL 14: Jueyinshu (BL 14); BL 15: Xinshu (BL 15); HT 7: Shenmen (HT 7); PC 6: Neiguan (PC 6); LI 4: Hegu (LI 4); TE 5: Waiguan (TE 5); LI 11: Quchi (LI 11); PC 7: Daling (PC 7); LU 11: Shaoshang (LU 11); PC 9: Zhongchong (PC 9); HT 9 : Shaochong (HT 9); PC 5 : Jianshi (HT 9); ST 36: Zusanli (ST 36); KI 3: Taixi (KI 3); SP 6: Sanyinjiao (SP 6); ST 40: Fenglong (ST 40); GB 39: Xuanzhong (GB 39); LR 3: Taichong (LR 3); SP 10: Xuehai (SP 10); KI 4: Dazhong (KI 4); KI 1: Yongquan (KI 1); BL 58: Feiyang (BL 58); SP 3: Taibai (SP 3). AD: Alzheimer's disease; GV: Governor Vessel; EX-HN: extraordinary acupoint; GB: Gallbladder Meridian of Foot Shaoyang; BL: Bladder Meridian of Foot Taiyang; ST: Stomach Meridian of Foot Yangming; LI: Large Intestine Meridian of Hand Yangming; CV: Conception Vessel; HT: Heart Meridian of Hand Shaoyin; PC: Pericardium Meridian of Hand Jueyin; TE: Triple Energizer of Hand Shaoyang; LU: Lung Meridian of Hand Taiyin; KI: Kidney Meridian of Foot Shaoyin; SP: Spleen Meridian of Foot Taiyin; LR: Liver Meridian of Foot Jueyin.

functional constipation: A randomized trial. *Ann Intern Med* 2016; 165(11): 761-769.

6 **Zhao L**, Chen J, Li Y, et al. The long-term effect of acupuncture for migraine prophylaxis: A randomized clinical trial. *JAMA Intern Med* 2017; 177(4): 508-515.

7 **Zhou J**, Peng W, Xu M, et al. The effectiveness and safety of acupuncture for patients with Alzheimer disease: A systematic review and Meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2015; 94(22): e933.

8 **Xue WG**, Zhang Z, Bai LM, et al. Effect of electroacupuncture on the behavior and the expression of amyloid beta-protein, amyloid precursor protein and ChAT in APP 695 V 717 I transgenic mice. *Zhen Ci Yan Jiu* 2009; 34(3): 152-158.

9 **Gao S**, Kong LH, Yu CC, et al. Mechanism of different frequencies of electroacupuncture in treating neuropathy inrats with Alzheimer's disease. *Zhong Guo Quan Ke Yi Xue Za Zhi* 2017; 20(12): 1449-1456.

10 **Shen MH**, Tang QQ, Li ZR, et al. Effect of electroacupuncture on hippocampal LTP in Alzheimer' s disease rats induced by Abeta (25-35). *Zhen Ci Yan Jiu* 2010; 35(1): 3-7.

11 **Wu G**, Li L, Li HM, et al. Electroacupuncture ameliorates spatial learning and memory impairment *via* attenuating NOX2-related oxidative stress in a rat model of Alzheimer's disease induced by Abeta1-42. *Cell Mol Biol (Noisy-le-grand)* 2017; 63(4): 38-45.

12 **Ma TT**, Yu SY, Li Y, et al. Randomised clinical trial: an assessment of acupuncture on specific meridian or specific acupoint vs. sham acupuncture for treating functional dyspepsia. *Aliment Pharmacol Ther* 2012; 35(5): 552-561.

13 WHO Regional Office for the Western Pacific. WHO standard acupuncture point locations in the Western Pacific Region. Geneva: World Health Organization, 2008: 1-108.

14 **Witten IH**, Frank E, Hall MA, et al. Data Mining: Practical machine learning tools and techniques. 2nd ed. Massachusetts: Morgan Kaufmann, 2016: 105-118.

15 **Fang JL**, Jin Z, Wang Y, et al. Comparison of central effects of acupuncture Taichongand nearby two acupoints by functional MRI. *Chin J Med Imaging Technol* 2005; 21(9): 1332-1336.

16 **Zhu B**, Wang Y, Zhang G, et al. Acupuncture at KI3 in healthy volunteers induces specific cortical functional ac-

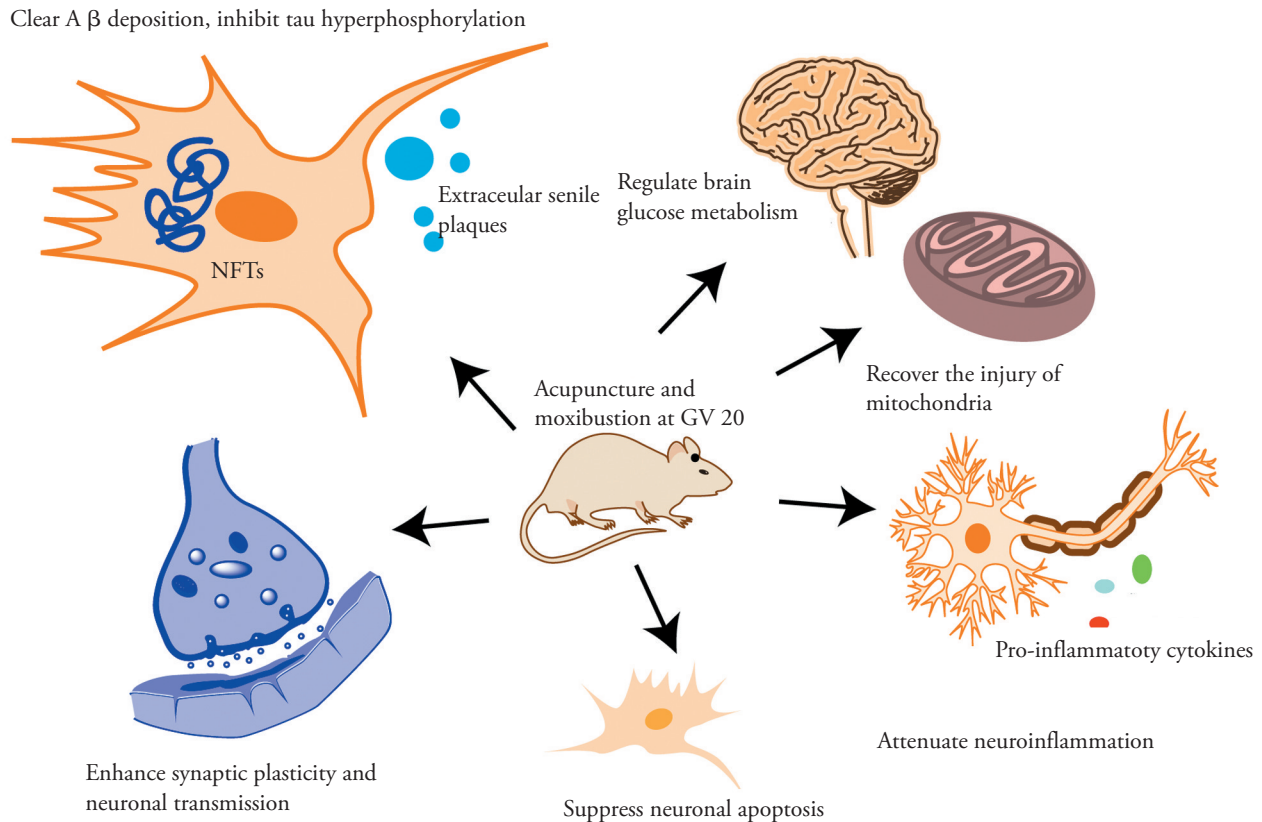


Figure 4 Possible underlying mechanisms of acupuncture and moxibustion at Baihui (GV 20)-centered combined-acupoints in AD model

Acupuncture and moxibustion at Baihui (GV 20) or Baihui (GV 20) centered acupoint combinations can ameliorates cognitive impairment of AD animal model *via* following pathways such as clear A β deposition, inhibit neurofibrillary tangles aggregation, enhance synaptic plasticity, regulate brain glucose metabolism, attenuate neuroinflammation, recover mitochondria injury and suppress neuron apoptosis based on current evidence. AD: Alzheimer's disease.

- tivity: an fMRI study. *BMC Complement Altern Med* 2015; 15: 361.
- 17 **Lan L**, Chang XR, Yan J, Wang et al. Influence of acupuncture on specific acupoints of Foot-Yangmingmeridian on patients with functional dyspepsia. *Zhong Guo Kang Fu* 2010; 25(1): 30-31.
 - 18 **Zhang J**, Zheng Y, Wang Y, et al. Evidence of a synergistic effect of acupoint combination: A resting-state functional magnetic resonance imaging study. *J Altern Complement Med* 2016; 22(10): 800-809.
 - 19 **Su Q**, Zhang JM, Li M. Application of functional magnetic resonance imaging in acupoint functional significance of encephalic region. *Zhong Guo Zhen Jiu* 2014; 34(5): 517-520.
 - 20 **Ma YX**, Ye XN, Liu CZ, et al. A clinical trial of acupuncture about time-varying treatment and points selection in primary dysmenorrhea. *J Ethnopharmacol* 2013; 148(2): 498-504.
 - 21 **Alizadeh R**, Esmaceli S, Shoar S, et al. Acupuncture in preventing postoperative nausea and vomiting: efficacy of two acupuncture points versus a single one. *J Acupunct Meridian Stud* 2014; 7(2): 71-75.
 - 22 **Wang Y**, Li W, Zhang KK, et al. Effect of electroacupuncture with different frequencies on learning and memory ability and synapse in hippocampus in rats with Alzheimer's disease. *Zhong Guo Kangfu Lilun Yu Shi Jian* 2016; 22(6): 635-639.
 - 23 **Zhang KK**, Kong LH, Wang Y, et al. Effects of electro-acupuncture of different frequency on the SYN protein and PSD-95 protein expression of rats with Alzheimer's disease. *Shi Zhen Guo Yi Guo Yao* 2016; 27(10): 2539-2542.
 - 24 **Li W**, Kong LH, Wang H, et al. High-frequency electroacupuncture evidently reinforces hippocampal synaptic transmission in Alzheimer's disease rats. *Neural Regen Res* 2016; 11(5): 801-806.
 - 25 **Zhu SX**, Sun GJ. Effects of electroacupuncture on learning and memory ability and glial cells of the hippocampus in the rat of Alzheimer disease. *Zhong Guo Zhen Jiu* 2009; 29(2): 133-136.
 - 26 **Luo L**, Sun GJ, Du YJ. Effect of "Kidney-reinforcing and Governor Vessel-regulating" of Acupuncture plus Moxibustion on Mitochondrial Dynamics-related Proteins in Hippocampal Neurons of Rats with Alzheimer's Disease. *Zhen Ci Yan Jiu* 2015; 40(4): 270-274.
 - 27 **Sun GJ**, Luo L, Du YJ, et al. Protective mechanism of acupuncture-moxibustion on hippocampal neuron mitochondria in rats with Alzheimer's disease. *Zhong Guo Zhen Jiu* 2014; 34(2): 157-162.
 - 28 **Guo HD**, Zhu J, Tian JX, et al. Electroacupuncture improves memory and protects neurons by regulation of the autophagy pathway in a rat model of Alzheimer's disease. *Acupunct Med* 2016; 34(6): 449-456.
 - 29 **Guo HD**, Tian JX, Zhu J, et al. Electroacupuncture suppressed neuronal apoptosis and improved cognitive impairment in the ad model rats possibly *via* downregulation of

- notch signaling pathway. *Evid Based Complement Alternat Med* 2015; 2015: 393569.
- 30 **Cao J**, Tang Y, Li Y, et al. Behavioral changes and hippocampus glucose metabolism in APP/PS1 transgenic mice *via* electro-acupuncture at governor vessel acupoints. *Front Aging Neurosci* 2017; 9: 5.
- 31 **Dong WG**, Lin L, Wang F, et al. Effects of electroacupuncture on the function of respiration chain in hippocampal mitochondria of SAMP8 mice. *Zhong Guo Zhen Jiu* 2012; 32(8): 726-730.