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ACUPUNCTURE FOR ALZHEIMER'S DISEASE

An investigation into essential combinations and methods

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ABSTRACT: Alzheimer's disease (AD) is the most prevalent form of dementia, with a devastating impact on the patient and their caregivers, while posing a tremendous challenge to the healthcare system. A definite cure is still a subject of research, with treatments being able to delay the progress of the disease, if only to a certain extent. In the past years acupuncture has been continuously considered for the treatment of AD due to its safety, cost-effectiveness and ease of application. In this review, recent studies ranging from 2018-2023 are analysed, acupuncture points, techniques, and treatment protocols that hold promise in addressing the various aspects of AD. An analysis and evaluation of the results will follow. TCM has a long history of treating dementia according to its principles, and the pathological process according to TCM principles such as yin-yang theory and pattern differentiation will be presented. Finally, from the data extracted an attempt will be made to define the essential parameters of treatment such as duration, frequency, and type of stimulation. Additionally, a brief investigation into other type of treatments within the TCM scope will follow.

1. Introduction

According to the WHO there are currently about 55 million people with dementia, 60% of which are living in low or middle income societies, with the numbers expected to surge to 78 million by 2030, and 139 million by 2050,[1] with AD and other dementias becoming the 7th leading cause of death worldwide.[2]. Caring for people with dementia carries a huge economic burden with the cost expected to reach 15.6 billion euros by 2030 in the Netherlands alone.[3]

Currently, there is no definite cure for AD. Pharmaceutical treatment merely addresses the symptoms of the disease and to some extent delays its pathological progress. Unfortunately these treatments are not without side-effects.[4] Due to the coexistence of AD with other diseases and pathologies, depression and hypertension being among them, timely prevention might be of essence to avoid the need for excessive medication. Polypharmacy is common in the aging population[5], and it may have detrimental results for the individual regardless of the existence of AD, but more so together with it.[6] This shows the need for interventions that cause fewer side-effects and exert a lower metabolic cost for the patient.

Acupuncture has proven to be a safe and effective treatment for AD, with few – if any – side effects,[7] however the mechanisms through which it achieves its results need further elucidation. This review aims to provide an explanation of the current most frequently employed combinations and techniques, summarize their clinical outcomes, analyze their efficacy, and discuss their potential in the future direction of acupuncture in the acupuncture treatment of AD.

2. Methods

2.1 Literature Search

To obtain relevant studies the method of internet search was employed. Google scholar (https://scholar.google.com/) was the main search engine used, with the CNKI journal translation project (https://jtp.cnki.net/bilingual/) being searched to find articles that were originally in Chinese and translated to English. Supplementary studies were found through references in other studies and systematic reviews. The terms searched for were 'acupuncture' or 'electroacupuncture' in combination with any of the following terms: 'Alzheimer's disease', 'AD', 'dementia', 'cognitive impairment', 'MCI', 'cognitive dysfunction' etc. Additionally, the term 'acupuncture' or 'electroacupuncture' was used in combination with terms related to the AD pathological process e.g. 'a7nAChR', 'oxidative stress', 'NLRP3' etc.

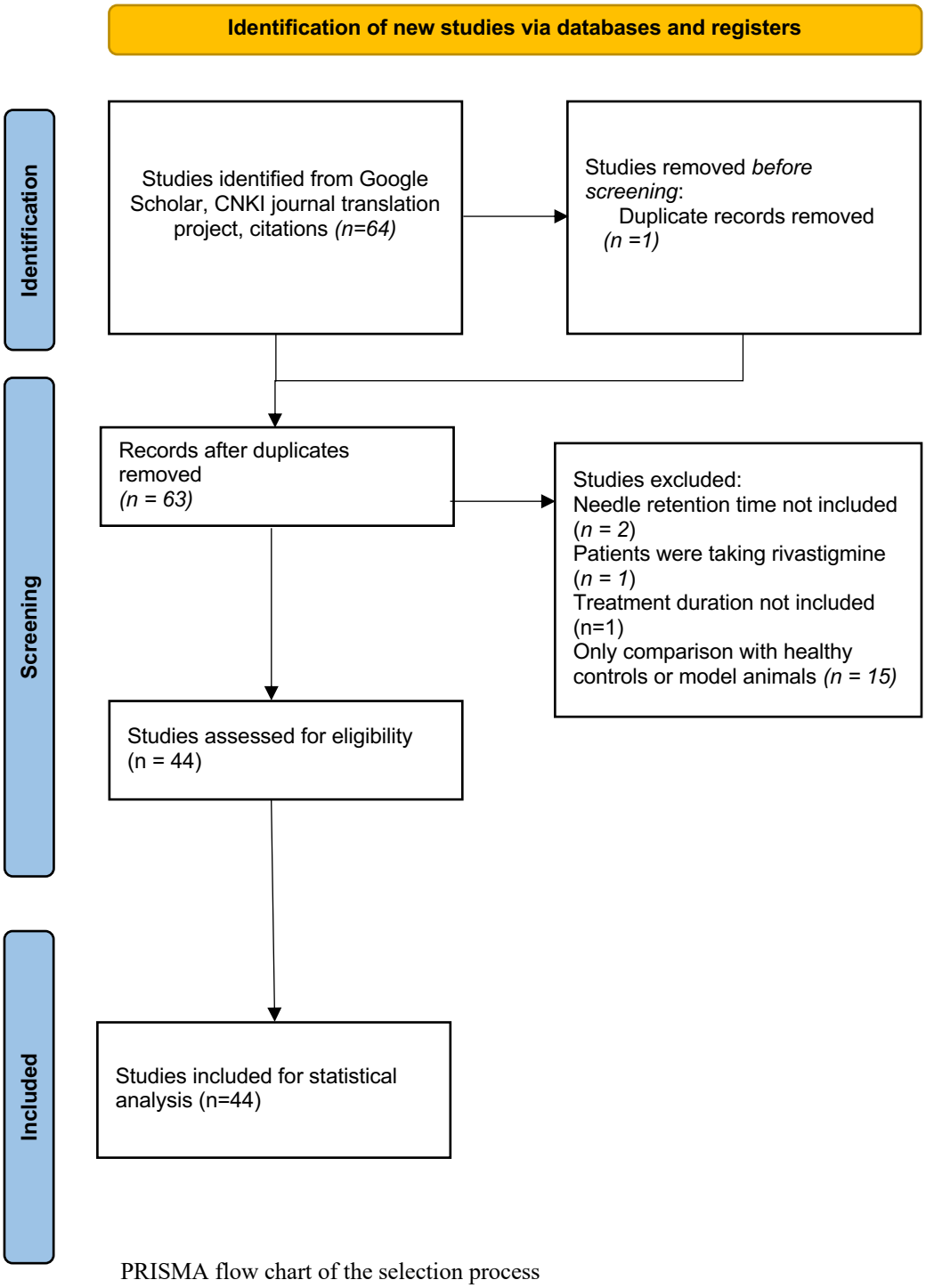
2.2 Inclusion and Exclusion Criteria

Studies were then filtered according to the criteria below:

1- Only studies within the 2018-2023 time frame will be included.
2- Studies should only be in the English language.
3- Must be published in a peer reviewed journal
4- Studies should only be using EA or MA
5- Studies should have the results of cognitive tests to verify the diagnosis, e.g. Morris water maze, open field test etc. for animals, MMSE, MoCA etc. for humans
6- Methods: a) Studies must involve either sham-acupuncture comparison, medication comparison, acupuncture combined with medication, an agonist or antagonist experiment to verify the effects of acupuncture, comparison of different EA frequencies, or EA/MA comparison.
   b) Human patients should not be receiving any medical treatment that would affect the results of the study.
   c) fMRI studies can still be included if the above do not apply, but they need to provide clear diagnostic criteria, and conform to criterion b).
7- Must conform to the STRICTA guidelines with a score of 4/6.

Excluded were the studies that presented with the following:

1- Studies not including essential treatment parameters. Those are EA frequency, wave, duration of treatment, duration of each session.
2- Studies including only comparison with healthy or model groups.



PRISMA flow chart of the selection process

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

2.3 Data Processing

In total, 44 studies were found eligible. The data from these studies were entered into a table in Microsoft Excel with the following parameters: *Author, Title, Year, Model, Sex, Sample size, Sham acupuncture, Controls, Drug intervention, Drug and acupuncture intervention, Healthy control group, Name of acupuncture method, Points, Method, Wave, Frequency, Intensity, Manipulation, Needling depth, Needle thickness, Treatment duration, Treatment frequency, Needle retention, Total number of treatments, Evaluation methods.* Functions of Microsoft Excel were used to extract statistical data and numerical values were rounded up to 1 decimal point.

3. Results And Statistical Analysis

3.1 Analysis And Comparison Between Human And Animal Studies

Out of the 44 studies, 31 (69%) were conducted using EA and 14 (31%) used MA, with an averaging a 4.4 week duration, 5.8 times per week, 25.2 min. needle retention, with the average total number of treatments being 22. 36 of 44 (82%) were animal studies while 8 (17%) involved human subjects.

The use of EA acupuncture was prevalent in both groups. In animal studies, it was used in 27 (69%), while in human studies in 5 (63%). Respectively, 12 (31%) animal studies and 3 (38%) human studies used MA.

In animal studies, the treatment duration was 3.6 weeks, 6.1 times per week, lasting 24.3 minutes, for a total of 20 treatments on average, while in humans treatment duration was 9 weeks, 4 times per week, lasting 32 minutes, for a total of 34.3 treatments on average.

Table 1. Statistical analysis of the total studies and comparison between human and animal studies.

	Total	***Percentage (%)***	***EA***	***Percentage (%)***	***MA***	***Percentage (%)***	***Average Treatment duration (weeks)***	***Average Treatment frequency (times per week) ****	***Average needle retention time (min.)***	***Average total number of treatments***
Total studies	44	100%	31	69%	14	31%	4.4**	5.8**	25.2**	22**
Animal `	36	82%	25	69%	11	31%	3.6	6.1	24.3	20
Human	8	17%	5	63%	3	38%	9**	4.0	32.0	34.3

**Treatments with a 15-day duration were rounded to two weeks, with treatment frequency and number of treatments remaining unchanged. ** Two single-treatment fMRI studies were excluded*

3.2 Methodological Analysis

The comparison of acupuncture with medication was performed in 4 out of 8 human studies (50%) and only in 11 out of 39 (28%) of animal studies. Studies including an experimental group to combine acupuncture and medication were 2 (25%) human and 1 (3%) animal.

Table 2. Analysis of methodology

	No. of Studies	***Comparison with medication***	***Percentage (%)***	***Combination of medication and acupuncture***	***Percentage (%)***
Human	8	4	50%	2	25%
Animal	36	9	25%	1	3%

3.3 Combination Frequency Analysis

Next, the frequency of each combination was counted and the results were inserted into Table 3. A total of 26 different combinations were found, with the lowest occurrence being 1 for most, and the highest 5. The average amount of times a single combination was found was 1.8 (3.8%), and the results of the studies using these combination will be presented.

3.4 Point Frequency Analysis

29 different points were used in total. GV20 Baihui was most commonly used point, found in 35 (76.1%) of the studies, with the next one being GV24 Shenting, which was used in 14 (30.4%). The top five acupoints were (in descending order) GV20, GV24, ST36 Zusanli, GV29 Yintang, and GV26 Shuigou. Details about the frequency of appearance of single points are in Table 4.

Table 3. Frequency of point combinations

	Combination	Frequency	Frequency rate
1	GV20, GV24	**5**	**11.4%**
2	GV20, ST36	**5**	**11.4%**
3	GV20, BL23	**4**	**9.1%**
4	GV20	**3**	**6.8%**
5	GV20, HN3	**3**	**6.8%**
6	GV24, GB13	**3**	**6.8%**
7	GV20, HN3, GV26	**2**	**4.5%**
8	LV3, LI4	**2**	**4.5%**
9	CV6, CV12, CV17, ST36, SP10	**1**	**2.3%**
10	GV20, GV14	**1**	**2.3%**
11	GV20, BL23, KD3	**1**	**2.3%**
12	GV20, CV17, BL17, CV6, SP6	**1**	**2.3%**
13	GV20, GV14, GV16	**1**	**2.3%**
14	GV20, GV14, GV16, GV26	**1**	**2.3%**
15	GV20, GV16	**1**	**2.3%**
16	GV20, GV24, GV16, HN3 (shangyintang), KD4	**1**	**2.3%**
17	GV20, GV24, GV26, HN3, HN1, GV17, GB20, HT7, SP6	**1**	**2.3%**
18	GV20, GV24, HN1, HN3, GB12, HT7, KD6, GB39	**1**	**2.3%**
19	GV20, GV24, HN3, HN1, HN54, HT7, LI4, LV3, SP6	**1**	**2.3%**
20	GV20, GV24, ST36	**1**	**2.3%**
21	GV20, LI4, ST36, SP6, BL13, BL20, BL23	**1**	**2.3%**
22	GV20,GV24, HN1, GB20	**1**	**2.3%**
24	HN3, LI20	**1**	**2.3%**
25	ST36	**1**	**2.3%**
26	ST36, SJ5	**1**	**2.3%**

3.5 Simultaneous Use Of Points Analysis

The co-existence of certain points was not limited only to the studies in which their effects as a single pair or combination was studied, but frequently appeared together with other points. For example, although GV20 and GV24 as a point pair was included in 5

studies, they appeared in total 11 times along with other points, meaning that while these two points were examined as an point-pair in 10.6% of the studies, they appeared together in 23.4%, which is more than double. Similarly, HN3 appeared in total 8 times, with 3 of these times being included with HN1 Sishencong in the treatment protocol, all of these including GV20, while GV20 and HN3 were a found together 9 times in total. These findings highlight the co-existence of certain points in various studies, even if they are not the main point pair. An analysis of the 11 most frequent common appearances of points is presented above in Table 5. A presentation of the findings amongst the most frequent combination is presented in table 7-16.

Table 4. Analysis of single-point frequency

	Point	Frequency	Frequency rate (%)
1	GV20	**35**	**76.1%**
2	GV24	**14**	**30.4%**
3	ST36	**11**	**23.9%**
4	HN3	**8**	**17.4%**
5	GV26	**4**	**8.7%**
6	SP6	**4**	**8.7%**
7	BL23	**4**	**8.7%**
8	LI4	**4**	**8.7%**
9	HN1	**4**	**8.7%**
10	GV16	**4**	**8.7%**
11	LV3	**3**	**6.5%**
12	GV14	**3**	**6.5%**
13	CV6	**3**	**6.5%**
14	CV17	**3**	**6.5%**
15	HT7	**3**	**6.5%**
16	GB13	**3**	**6.5%**
17	CV12	**2**	**4.3%**
18	GB20	**2**	**4.3%**
20	KD3	**1**	**2.2%**
21	SJ5	**1**	**2.2%**
22	BL17	**1**	**2.2%**
23	KD4	**1**	**2.2%**
24	GV17	**1**	**2.2%**
25	KD6	**1**	**2.2%**
26	GB39	**1**	**2.2%**
27	HN54	**1**	**2.2%**
28	BL13	**1**	**2.2%**
29	BL20	**1**	**2.2%**

Table 5. Analysis of point coexistence

	Points	Frequency	Frequency rate
1	GV20, GV24	**11**	**23.4%**
2	GV20, HN3	**9**	**19.1%**
3	GV20, ST36	**7**	**14.9%**
4	GV20, BL23	**6**	**12.8%**
5	GV20, GV26	**4**	**8.5%**
6	GV20, SP6	**4**	**8.5%**
7	GV20, GV24, HN1	**4**	**8.5%**
8	GV20, HN1	**4**	**8.5%**
9	GV20, GV16	**4**	**8.5%**
10	HN1, HN3	**3**	**6.4%**
11	LV3, LI4	**3**	**6.4%**
12	GV20, GV12, GV16	**3**	**6.4%**

Table 7. Methods and findings of studies using GV20, GV24

Author	***Sample Size and Model***	***Method***	***Treatment parameters***	***Treatment frequency and duration***	***Outcomes***
Li, 2020[8]	48 APP/PS1 mice	EA	Disperse/dense wave @ 1/20 Hz	30 minutes/3 days a week for 16 weeks	• MWM: improved escape latency and space exploration in both mild and moderate AD. • Plaque number and area fraction in PtA and Ent: both reduced in the PtA of mild AD mice, plaque number reduced in PtA and Ent of moderate AD mice, with no effect in area fraction. • IL-1β and iNOS mRNA expression levels reduced only in mild AD mice.
Li, 2021[9]	PS-cDKO mice	EA	Continuous wave @ 2 Hz	15 minutes/5 days a week for 3 weeks	• Improved preference degree and recognitive index in NOR test. • Increased the duration of entering the new arm in the Y-maze • Improved escape latency and space exploration in MWM • Reversed p-Tau levels • Suppressed IL-1 β and IL-18 levels • Inhibited NLRP3 inflammasome • Increased LTP induction by high-frequency stimulation • Restored NR1, NR2A, and NR2B levels
Ma, 2022[10]	48 pBCCAO rats	EA	Continuous @ 2 Hz	30 minutes daily for 2 weeks	• Improved escape latency and space exploration in MWM • Decreased apoptotic neurons in the frontal cortex • Reduced IL-16 levels • Increased PSD-95 and miR-81 levels in the frontal cortex

Table 7. Methods and findings of studies using GV20, GV24

Dai, 2022[11]	60 pBCCAO rats	EA	Disperse/dense wave @ 2/20 Hz	30 minutes/5 days a week for 4 weeks	• Improved escape latency and space exploration in MWM • Increased fEPSP slope (LTP), increased fEPSP amplitude • Upregulated decay and rise times of sEPSCs in the hippocampus • Increased pGluR1 and pNMDAR2B and CaMKII
Lin, 2022[12]	40 3x-Tg AD mice	EA	Disperse/dense wave @ 1/20 Hz	20 minutes/5 days a week for 4 weeks	• Time spent exploring the novel object and the number of visits increased in the NOR test • Increased regional spontaneous activity in the amygdala, auditory cortex, DG, dorsal raphe nucleus, EC, hippocampus, somatosensory cortex, subiculum, substantia nigra, temporal cortex, and ventral tegmental area. • Improvement of postsynaptic sEPSC of the hippocampus CA1 area • Positive correlation between differences in recognition index (time/number) and ReHo values of the hippocampus and entorhinal cortex • positive correlation between difference in NORT performance (recognition index of time) and FC strength between the hippocampus and entorhinal cortex • Increased nerve fiber connection between hippocampus and entorhinal cortex • positive correlation between difference in NORT performance and the number of nerve fiber connections between the hippocampus and EC

Table 8. Methods and findings of studies using GV20, ST36

Author	***Sample Size and Model***	***Method***	***EA parameters***	***Treatment frequency and duration***	***Outcomes***
Hou, 2020[13]	30 SAMP8 mice	EA	Continuous wave @ 2 Hz (first group) And 10 Hz (second group)	30 minutes every day for 2 weeks	• Improved escape latency and space exploration in MWM • Decreased serum IL-1β, IL-6, IL-18, and TNF-α levels with both frequencies • 10 Hz EA decreased serum IL-1β and IL-6 levels more than 2 Hz • 10 Hz EA reduced the apoptotic cells in the CA1 region more than 2 Hz • NLRP3/caspase-1 pathway-related proteins significantly downregulated by EA • 2 Hz EA did not effectively reduce ASC protein expression • Both frequencies failed to reduce the expression of Aβ and tau proteins
Wang, 2020[14]	24 pBCCAO rats	MA	- Twirling-reinforcing 120 days/minute for 1 minutre	10 minutes/6 days a week for 2 weeks	• TNF-a, IL-6 decreased in the hippocampus and plasma • TLR4 and TLR2 protein and mRNA levels reduced • myD88/NF-kB was inhibited • miR-93 was decreased
Cao, 2020[15]	24 pBCCAO rats	MA	-	10 minutes/6 days a week for 2 weeks	• Improved escape latency and space exploration in MWM • Alleviated neuronal injury in the hippocampus • Downregulation of TNF-a, IL-6 • a7nAChR protein and mRNA upregulation in the hippocampus • JAK2/STAT3 phosphorylation increased

Table 8. Methods and findings of studies using GV20, ST36

Ma, 2020[16]	40 BCCAO rats	MA	-	15 minutes/6 days a week for 2 weeks	• Time spent exploring the novel object and the number of visits increased in the NOR test • Improved escape latency in MWM • Improved white matter CBF in corpus callosum and entorhinal cortex • Improved white matter integrity • Prominent reduction in fiber attenuated by acupuncture • IL-1β and IL-6 levels were restored to the levels of the sham-surgery group
Xiao, 2018[17]	BCCAO rats	MA	-	10 minutes/6 days a week for 2 weeks	• Increased exploratory activity in NOR test • Improved spatial memory in RAM test • Elevated population spike in the dentate gyrus • elevated expression of dopamine-β-hydroxylase in the hippocampus and CSF

Table 9. Methods and findings of studies using GV20, BL23

Author	***Sample Size and Model***	***Method***	***EA parameters***	***Treatment frequency and duration***	***Outcomes***
Yang, 2018[18]	48 APP/PS1 mice	EA	Continuous wave @ 2 Hz	15 minutes/6 days a week for 2 week	• Improved escape latency and space exploration in MWM with 3 course EA better that 2 course EA • Downregulated APP and BACE1 with 3 course EA better than 2 course EA • Increase IDE expression with 3 course EA better than 2 course EA
Yu, 2020[19]	48 D-galactose injected rats	EA	Continuous wave @ 50 Hz	20 minutes/6 days a week for 8 weeks	• Improved escape latency and space exploration in MWM • Ameliorated loss of dendritic spines • Neuronal microtubules were longer and less fractured with increased density of the microtubules in the hippocampus • Improved tau hyperphosphorylation • Increased expression levels of PSD95 and synapsin-1 in the hippocampus
Yu, 2020[20]	72 D-galactose injected rats	EA	Continuous wave @ 50 Hz	20 minutes/6 days a week for 8 weeks	• Improved escape latency and space exploration in MWM. • Improved tau hyperphosphorylation with EA performing better than MA • Inhibited GSK-3β • Upregulated DNMT1

Table 9. Methods and findings of studies using GV20, BL23

Yu, 2018[21]	56 Amyloid injected rats	EA	Continuous wave @ 2, 30, and 50 Hz	20 minutes/6 days a week for 8 weeks	• Improved escape latency and space exploration in MWM, with 50 Hz having the biggest effect • Higher synaptic curvatures, lower width of the synaptic cleft with frequency not being a factor. postsynaptic densities were thicker, with the 50 Hz treatment having the biggest effect • Significantly reduced total GSK-3β, p-GSK-3β (Tyr216), and APP levels and increased p-GSK-3β (Ser9) level. Effects was frequency dependent, with 50 Hz having the greatest effect • Decreased expression of $A\beta_{1-40}$. 50 Hz had the greatest effect

Table 10. Methods and findings of studies using GV20

Author	***Sample size and Model***	***Method***	***Treatment parameters***	***Treatment frequency and duration***	***Outcomes***
Lin, 2018[22]	36 APP/PS1 mice	EA	Dense/disperse wave @ 1/20 Hz	30 minutes/every day for 4 weeks	• Improved escape latency and step-down avoidance in MWM • Increased NAA and Glu levels • Increased neuronal survival in CA1 and CA3 areas • Upregulated BNDF/TrkB pathway
Ma, 2019[23]	MCAO rats	EA	Dense/disperse wave @ 2/15 Hz	Surgery pre-treatment lasting 30 minutes for 5 days	• smaller infarction volume • improved neurological scores after stroke • increased a7nAChR expression in the ischemic penumbra • microglial M1 markers iNOS and IL-1b were decreased and M2 markers Arg-1 and TGF-b1 increased • TNF-a decreased and IL-10 increased, agonist/antagonist confirmed a7nAChR involvement in microglial conversion
Li, 2020[24]	100 MCAO rats	MA	Needle rotated for 1 min at a frequency of 200 rpm, once per hour	2 hours every day for 3 weeks in combination with exercise	• Modified Bederson's neurological function scale scores improved. • Decreased infract size • Decreased caspase-3 and Bax levels • TNF-a, IL-1b and ROS levels decreased • Higher number of BDNF, S100b and GFAP positive cells

Table 11. Methods and findings of studies using GV20, HN3

Author	***Model and Sample Size***	***Method***	***Treatment parameters***	***Treatment frequency and duration***	***Outcomes (GV20, HN3)***
Li, 2020[25]	30 SAMP8 mice	EA	Sparse wave @ 2 Hz	15 minutes/every day for 15 days	• Improved escape latency and space exploration in MWM • Improved hippocampal neuronal structure, with appearance similar to the control group • Higher hippocampal TREM2 protein
Jiang, 2021[26]	32 SAMP8 mice	EA	Sparse wave @ 2 Hz	15 minutes/every day for 15 days	• Improved escape latency and space exploration in MWM • Improved neuron structure in the frontal lobe • Improved gut microbiota composition but only in 3 species • Lower IL -1β, IL-6 and TNF-α levels in serum and hippocampus
Ding, 2019[27]	30 SAMP8 mice	MA	Twirling bi-directionally within 90 degrees with a speed of 180 degrees/second, every 5 min for 15s.	20 minutes every day for 2 weeks	• Improved MWM scores • Improved cerebral blood flow in the prefrontal lobe and the hippocampus

Table 12. Methods and findings of studies using GV20, HN3, GV26

Author	***Model and Sample Size***	***Method***	***Treatment parameters***	***Treatment frequency and duration***	***Outcomes***
Tang, 2020[28]	40 APP/PS1 mice	EA	Continuous wave @ 1 Hz with pricking method at GV26	20 minutes/3 days a week for 4 weeks	• Lower escape latency, number of platform crossings, time spent in target quadrant in MWM • Lower APP deposition • Reduced MKK4, MKK7, c-Jun and caspase-3 expression • Lower p-MKK7, c-Jun expression • Reduced JNK phosphorylation
Lu, 2019[29]	36 APP/PS1 mice	EA	Continuous wave @ 2 Hz with pricking method at GV26	20 minutes every day for 15 days	• Improved MWM scores • Reduced microglial activation in the hippocampus • Reduced TLR4-, NF-kB- and iNOS-immunoreactive cells and protein expression

Table 15. Methods and findings of studies using GV24, GB13

Author	***Model and Sample Size***	***Method***	***Treatment parameters***	***Treatment frequency and duration***	***Outcomes***
Zhang, 2019[30]	56 D-galactose injected	MA	twisting frequency of 80± 5/min, a twisting amplitude of 180°±5°, and a sustainable stimulation for 2 min, with 1 min rest;	15 minutes/6 days a week for 4 weeks	• Improved behavioural performance in the escape/avoidance test • Concentrations of Ache, ChE, chAT, MDA and ROS were decreased. SOD was increased • Improved hippocampal neuronal structure • Inhibition of Bax, CYC, caspase-3, caspase-9 and activation of Bcl-2
Yang, 2020[31]	60 D-galactose injected	EA	Continuous wave @ 30 Hz	30 minutes/ 6 days a week for 4 weeks	• lower duration spent in the central zone and higher frequency of crossing in the OFT • Decreased levels of Aβ, p-tau (s396) and p-tau (s404) in the hippocampus
Zheng, 2021[32]	5xFAD (Tg)	EA	Continuous wave @ 2 Hz	15 minutes/ 5 days a week for 4 weeks	• Improved MWM scores • Decreased freezing time in FC test • reduced the levels of Fl-APP and c-terminal fragments in the prefrontal cortex and hippocampus • reduced the Aβ positive area and plaque size in the prefrontal cortex and CA1 regions • Activated TFEB and promoted lysosomal biogenesis • Inhibited microglial activation

Table 16. Methods and findings of studies using LV3, LI4

Author	***Model and Sample size***	***Method***	***Treatment parameters***	***Treatment frequency and duration***	***Outcomes (LV3, LI4)***
Shan, 2018[33]	49 Human MCI and AD patients	MA	rotated continuously (±180∘, 60 times per minute)	1 time treatment 3 minute stimulation	• Activated bilateral cerebellum, right inferior frontal gyrus (pars opercularis and pars orbitalis), right middle temporal gyrus, left pallidum, left rolandic operculum, left superior parietal gyrus, and left supramarginal gyrus. Decreased activation in the right cuneus, right pallidum, right inferior occipital gyrus, left rectus, left cerebellum, and left putamen in AD patients • Activated left supramarginal gyrus, left superior temporal gyrus, left rolandic operculum, left cerebellum, right middle frontal gyrus, and right inferior frontal gyrus (pars opercularis). Inferior parietal gyrus (BA40) showed decreased activity
Zheng, 2018[34]	28 Human AD patients	MA	No manipulation	1 time treatment 3 minute stimulation	• significantly increased ALFF in the left postcentral gyrus • right IFG, right hippocampus and MCC showed decreased ALFF after acupuncture • increased connectivity between the right hippocampus and the left precentral gyrus • Negative correlations between the AVLT scores and the ALFF values of the hippocampus and the right ITG. • Negative correlation between the AVLT scores and the connectivity of the right hippocampus and the left precentral gyrus • Positive correlations between the MMSE and MoCA scores and the ALFF values of the SCC

4. Discussion

4.1 Review Of Animal Studies

4.1.1 Acupuncture Enhanced Crucial Pathways For Neurogenesis

Acupuncture appears to influence the process of neurogenesis in animal models, potentially through BDNF modulation and its receptor TrkB. BDNF-TrkB signalling has been found to be essential in hippocampal neurogenesis and neuronal survival.[35] In MCAO rats, Li[24] observed that GV20 upregulated BDNF expression, while more significantly Lin observed that EA at GV20 can upregulate both BDNF/pTrkB in APP/PS1 mice.

Another critical factor for the activity-dependent integration of new neurons is the normal functioning of NMDA receptors.[36] Two studies found that EA at GV20 with GV24 was able to increase expression levels of NR1, NR2A, and NR2B in the hippocampus, the first in Ps-cDKO[37] mice and the second in BCCAO rats,[10] an event not only connected to neurogenesis, but also to neuronal survival and in the rescue of Aβ-mediated synaptic dysfunction, as the latter occurs through NMDA receptors.[38]

4.1.2 Neuroprotective Benefits Against Aging And AD

The PI3K/Akt pathway plays a role in many AD-related pathological processes. GSK3-β, a downstream target of PI3K/Akt, induces Tau hyperphosphorylation and a reduction of NMDA receptor subunits NR2A/B.[39]

Three studies have reported a decrease in GSK3-β phosphorylation in BCCAO[17], APP/PS1[40], and D-galactose injected[41] models respectively, which was accompanied by a reduction of phosphorylated Tau. Out of the three studies, only one reported the upregulation of Akt, however another study reported upregulation of the PI3K/Akt[42] but focused more on its effect on autophagy than the activation of GSK3-β. Although it cannot be certain that upregulation of GSK3-β in these models is BDNF- dependent, especially for the APP/PS1 mice, it seems that it may very well be the case for the BCCAO and D-galactose models. Inhibition of GSK3-β has further been found to have an effect on amyloid clearance,[43] so in the earliest stages of the disease which are more tau-dependent (ref-braak), the PI3K/Akt/GSK3-β pathway may represent a valid target of research concerning the effect of acupuncture.

In APP/PS1 mice, Yu[19] found that EA at GV20, BL23 reduced Tau phosphorylation at crucial sites, while downregulating mTOR, a fact that may influence a variety of pathological mechanisms. Huang[44] observed that EA at GV20, GV24, and ST36 produced decrease in p-p38MAPK in a hepatic encephalopathy mouse model with the study showing that treatment affected other crucial inflammatory pathways. The same occurred in SAMP8 mice with LI20 and HN3,[45] also accompanied by a decrease in amyloid deposition and tau hyperphosphorylation, while a third study in MCAO rats showed a similar effect using EA at GV20, PC6 and SP6,[46] along with a decrease in calpain expression, a culprit of prolonged NMADR activation induced mitochondrial dysfunction and apoptosis.[47]

Multiple studies reporting an increase in TUNEL-positive neurons in the hippocampus and cortex. Apoptosis is a central cell death mechanism in AD but whether its inhibition could provide therapeutic benefits is still a subject of research. It has been observed that senescent cells are resistant to apoptosis and instead necroptosis is favoured as a cell death mechanism, however it has been suggested that apoptosis can induce necroptosis provided that the ability of astrocytes to clear apoptotic cells is impaired.[48] Additionally, the pathways that trigger both types of cell death are similar. The induction of apoptosis may come about through multiple mechanisms, including amyloid toxicity, inflammation, and inactivation of a7nAChRs,[49] as well as downregulation of PI3K/Akt,[50] all participating in the disease process.

In a D-galactose model, GV24 with GB13 modulated the key apoptosis-related proteins Bcl-2, Bax, and caspase-3 AD as reported by Zhang,[30] while in another study Li[24] used GV20 for 2 hours daily, increased BDNF, reduced inflammation and decreased both caspase-3 and Bax. Tang[28] observed that EA at GV20, GV29, and GV26 in APP/PS1 mice lowered the levels of a key modulator of apoptosis, JNK, stress-related kinase, by reducing the expression of its main activators MKK4 and MKK7.[51] JNK phosphorylation may be stimulated by increased production of excessive H_2O_2 by mitochondria,[52] and loss of trophic signalling,[53] while downstream effects involve tau hyperphosphorylation, Aβ generation, and activation of TLR4 signalling, as well as an overall contribution to the inflammatory process.[54] Mitochondrial dysfunction and oxidative stress are considered early-transpiring events in AD as well as components of the aging brain,[55] so perhaps intervention at those points may have neuroprotective effects at those stages. NAA is a marker of the functional integrity of neuronal mitochondrial metabolism and may be critical for myelinogenesis,[56] since its breakdown product, acetate, partakes in the production of myelin lipids. In a previously mentioned study, Lin[22] upregulated NAA together with BDNF-TrkB, in APP/PS1 mice using EA at GV20.

On the other hand, increased oxidative stress may trigger or exacerbate neuroinflammation in aging and AD. EA at GV20 and GV14 on BCCAO rats by Bi[57] increased the activity of antioxidant enzymes SOD and CAT while ROS and MDA contents were decreased along with improvements in GFAP expression and the number of apoptotic neurons. This study also further reported a downregulated NOX4 expression, a mediator of oxidative stress and apoptosis in brain inflammation and in aging-associated cardiovascular disease.[58] Although the BCCAO resembles the aging process and the circumstances of vascular cognitive impairment, this study may shed some light to the relationship between oxidative stress, inflammation, CCH, and aging, indicating how acupuncture may impact AD, as well as influence its risk factors before other pathogenic processes are more dominant. Similarly, Liu,[59] in a post-operative cognitive dysfunction rat model, higher SOD and lower MDA levels were found. In this study a decrease in IL-1β and TNF-a levels, and astrocyte numbers were observed while an increase was noted in serum BDNF and GDNF, and lower S100β levels. In AD patients, S100β expression correlates with the number of dystrophic neurites indicating that treatment supported the neuro-restorative process.[60] The use of EA at GV20 by Han[61] induced positive changes in the cholinergic activity (higher ACh content, and restoration of ChAT and AChE activities) accompanied by the increase in antioxidant CAT and GSH activity with associated decreases in MDA and H_2O_2 levels.

Another cause of neurodegeneration in the human brain in a chronic state of cerebral hypoperfusion, and has been well implicated in setting the stage for AD,[62] participating in the lowered energy metabolism, amyloid accumulation and tau hyperphosphorylation, generation of oxidative stress, as well as brain atrophy. Vascular dysfunction is prominent in prodromal AD and reduced CBF is correlates with the rate of amyloid deposition.[63] In SAMP8 mice, Ding[27] combined GV20 with GV29 improved to some extent the blood flow

to the prefrontal cortex, and while the results were similar compared to donepezil in that aspect, the mice exhibited higher improvement in the Morris water maze test, although both interventions failed in completely restoring CBF compared to healthy controls. Ma[16] in another study, GV20 with ST36 improved CBF in the white matter of BCCAO rats, improved white matter integrity, while reducing white matter inflammation and the associated markers TNF-a, IL-1β, and IL-6.

In contrast to familial-AD, the reason for the accumulation of amyloid deposits in late-onset AD is strongly hypothesized to be the dysfunction of the blood-brain barrier (BBB),[64] an event which is worsened by cerebral or systemic inflammation, since the pro-inflammatory microglial activation may impair their ability to clear Aβ. In LPS-induced cognitive dysfunction mice, GV20, GV29 and ST36 by Zhang[65] produced an improvement in the tight-junction structures in the hippocampus of and cortex, while positively regulating the gut microbiota. Regarding the clearance of Aβ from the brain, Yang[66] found that GV20 with BL23 elevated the expression of insulin-degrading enzyme (IDE) in APP/PS1 mice. This study, along with a few others have reported positive effects on APP expression, BACE1, Aβ, and the number of senile plaques. There were also other studies that improve gut microbiota composition and that could be beneficial as a prevention mechanism. However, a study by Li[8] investigated the effect of acupuncture on plaque number and are fraction in the parietal association cortex (PTA) and entorhinal cortex (ENT) of APP/PS1 mice, and observed no significant difference in plaque number in the moderate AD mice, while the effect on mild AD mice was confined in the PTA. Similar results were documented for microglial polarization, with acupuncture failing to upregulate the M2 microglial phenotype in moderate AD.

4.1.3 Effect On Neuronal And Synaptic Function

The basis of the cholinergic hypothesis is that the functional deficits observed in AD are caused by the loss of cholinergic neurons, and attenuated neurotransmission. Improvement in the cholinergic markers of LPS-induced cognitive impairment mice (increase in ACh content, and upregulation of ChAT and downregulation of AChE) was obtained by EA at GV20 by Han.[67] Of the acetylcholine receptors, the a7nAChR has been found to have influence in AD-related processes. The hippocampus is an area rich in a7nAChRs and upregulating their activity may provide protection against inflammation,[68] and Aβ mediated synaptic depression[69], by playing a crucial role in various downstream mechanisms. In male Wistar rats, an a7nAChR partial agonist completely rescued early and late LTP-impairment as induced by soluble Aβ oligomers, whereas donepezil did not as observed by Kroker.[70] It is supported that nAChRs exert their neuroprotective effect through the activation of PI3K/Akt pathway,[71] which leads to activation of Bcl-2. Warming-dredging needling at GV20, GV14 and GV26 by Yang[72] upregulated the a7nAChR expression in the hippocampus of BCCAO rats, while there were two studies that reported a concomitant attenuation of inflammation. In MCAO rats, pre-treatment with EA at GV20 by Ma[23] noted decreased iNOS and IL-1β levels and increased Arg-1 and TGF-b1, suggesting that stimulation of nAChRs by acupuncture contributed to the phenotypic conversion of microglia while puncturing GV20 and ST36 was found to increase the a7nAChR downstream in BCCAO rats by Cao.[15]

It is established that the degree of dementia is related to the synaptic loss between the basal forebrain and the hippocampus and cortex, and that the integrity of cognitive functioning

depends, to some extent, on the integrity and transmission efficiency of the synapses.[73] In 3xTg AD mice, Lin[12] applied EA at GV20, GV24 improved post-synaptic sEPSC in the CA1 area of the hippocampus together with an increased connectivity between the hippocampus and the entorhinal cortex. In BCCAO rats, GV20 and ST36 by Xiao[17] rescued the LTP deficit of the dentate gyrus while in the same model, EA at GV20 and GV24 by Dai[10] increased the fEPSP amplitude, and upregulated the decay and rise times of sEPSCs. In the same study, upregulation of GluR1, CaMKII and NR2B was also noted. In Aβ-injected rats, EA at GV20 and BL23 improved the synaptic ultrastructure in the hippocampus with higher synaptic curvatures, lower width of the synaptic cleft and thicker post-synaptic densities, with the study also reporting altered GSK-3β phosphorylation levels, and lower APP expression and Aβ expression.[74]

Contrary to the above, Cai[75] found that in 5xFAD Tg mice, KD3 enhanced the level of LTP in the prefrontal cortex but the effects did not reach statistical significance This effect was not present in the hippocampus in contrast to the previous studies, but it may be related to the differences of the model used, or perhaps to the choice of point. However, a significant increase in both synaptophysin and PSD-95 in the prefrontal cortex was recorded. PSD-95 is an important scaffold protein with multiple functions that eventually determine the synaptic response.[76] The same study observed significant reduction in APP, and a significant decrease in insoluble Aβ levels and plaques larger than 40 μm in the prefrontal cortex, but failed to do the same for the hippocampus, while also decreasing neuroinflammation in the PFC. Finally, the study revealed an increased glucose metabolism in the PFC and hypothalamus but not in the hippocampus. Two other studies also noted an upregulation of PSD-95. Wang[77] performed EA using the olfactory-three needle technique, which comprises of GV29 and LI20, and achieved this effect on the hippocampus of SAMP8 mice, while Ma[10] performing EA at GV20 and GV24, observed the same for the frontal cortex of BCCAO rats.

4.1.4 Acupuncture Modulates Key Inflammatory Pathways

Microglia are equipped with pattern recognition receptors (PRRs) which upon tissue damage put the production of inflammatory cytokines in motion. One PRR found to be chronically activated in AD, is the toll-like receptor-4 (TLR-4). Activated TLR-4 recruits myD88 which further activates the transcription factor NF-κB,[78] resulting in M1 type macrophage activation and in the production of the major inflammatory cytokines in AD, such as TNF-α, IL-1β, IL-6, IL-12, among others,[79] although in preclinical AD activation of NF-κB seems to have a neuroprotective role.[80] In a 4VO model (occlusion of the bilateral common carotid arteries and the vertebral arteries) EA at GV20 by Bu[81] combined with RN17, RN6, SP6 and BL17 inhibited the increase of the TLR4/myD88/NF-κB pathway, while the same result was also found in hepatic encephalopathy model rats by Huang[82] who used EA at GV20, GV24 combined with ST36 and in APP/PS1 mice by Lu[29] using EA at GV20, GV29 combined with the pricking method at GV26, and in BCCAO rats by Wang[14] using GV20 and ST36.

The NLRP3 inflammasome is responsible for pyroptosis and has received a lot of attention for AD and other neurodegenerative diseases. Several factors can accelerate or cause the activation of the NLRP3 such as high contents of IL-1β, CCH, apoptotic cell death pathways, increase in intracellular calcium, mitochondrial dysfunction-related ROS production,[83] as well as excessive $A\beta_{42}$ accumulation,[84] and priming by NF-κB. The NLRP3 inflammasome consists of sensors for DAMPs and PAMPs, the apoptosis-associated speck

like protein (ASC) and procaspase-1. Different combinations were found affecting the activation of NLRP3 inflammasome. In SAMP8 mice, EA at GV20 and ST36 reduced all three components of ASC/NLRP3/caspase-1 and observed a frequency-dependent effect, with 2 Hz EA failing to reduce ASC and not achieving the effect of 10 Hz EA for IL-1β and IL-6 together with NLRP3/caspase-1, as reported by Hou.[13] Despite this result, there was no significant difference observed in the Morris Water Maze. On the same model, EA GV20, GV29 with pricking at GV26 by Jiang[85] found a similar result. EA at SJ5 and ST36 on MCAO rats by Sha[86] and EA at GV20, GV24 on PS cDKO mice by Li,[87] reported similar benefits, although both of these studies found that treatment could influence IL-1β and IL-18 levels but did not alter TNF-α expression. In both studies the use of an NLRP3 inhibitor reversed the effects of acupuncture. It is worth mentioning that two of the studies included also measured the levels of p-Tau in the hippocampus, and while in SAMP8 mice EA did not significantly influence its levels, in Ps-cDKO mice the difference was significant, a result which certainly can be attributed to the choice of model and their characteristics, since the SAMP8 is an aging model while the Ps-cDKO is a model of AD pathology with emphasis on neuroinflammation.

There were other molecules and pathways associated with neuroinflammation which were affected by acupuncture treatment like the p38MAPK/STAT3 pathway,[88] S100β,[89] and TREM2.[25] In fact, a great percentage of the studies reviewed either dealt exclusively or included a measurement of inflammatory markers and cytokines (mostly IL-1β and TNF-a). Cellular senescence and oxidative stress are drivers of inflammation and both events occur in the aging brain.[90] In SAMP8 mice, EA at GV20, BL23 and KD3 by Xu[91] reduced GFAP and Iba1 protein levels which when combined with the effect on oxidative stress mentioned could exert a neuroprotective influence against the effects of aging.

4.1.5 Acupuncture Reduced Aβ Deposition And Tau Hyperphosphorylation

Amyloid plaque formation occurs mainly from the processing of APP through the amyloidogenic pathway largely mediated by the BACE 1 enzyme.[92] Once Aβ accumulation reaches a significant level, microglia are activated producing inflammatory cytokines that further stimulate amyloid deposition.[93] 2 Hz EA at GV20 and GV29 by Tang[28] combined with GV26 managed to achieve lower APP expression in APP/PS1 mice. Xu[94] used the same prescription on the same model and observed reduction of both $A\beta_{40}$ and $A\beta_{42}$ in the frontal lobe, together with marked glucose uptake, reduction of inflamed areas and the restoration of IL-1β and IL-10 to levels closer to normal in that area. Yet another study on the same prescription by Tang[95] (this time with EA at 1Hz) effectively reduced both APP and BACE1. In a study by Yang,[18] EA at GV20 and BL23 found that the reduction of APP/BACE1 was accompanied by the reduction of senile plaque number. This study further indicates that the clearance of Aβ was improved, as marked by the increased IDE expression. This study also compared different courses of treatment finding that the longer course achieved better results in the previous markers. Yu[96] used the same prescription in amyloid-injected rats to compare the effects of different EA frequencies, observing that 50 Hz EA reduced $A\beta_{1\text{-}40}$ expression and APP levels, and improved the thickness of the post-synaptic density more effectively than 30 Hz or 2 Hz. GSK-3β which is enhanced by Aβ deposition and mediates Tau hyperphosphylation was also found decreased. The AKT/GSK-3β pathway was also affected by EA at GV20, GV29 with GV26 with increased levels of p-AKT and P-GSK-3β being observed in APP/PS1 mice by Xu.[97] Marked reduction of p-Tau at key phosphorylation sites Ser199 and Ser202 and the improvement of glucose uptake in

the hippocampus was also noted. In Ps-cDKO mice, Li[98] observed the marked decrease of p-Tau levels, and the NLRP3 inflammasome.

4.2 Review of Human Studies

4.2.1 Acupuncture Modulates The Activity Of Certain Cerebral Areas Affected In AD

As mentioned, there is a reorganization in brain structure and function that is expressed through out of the ordinary increases and decreases of brain activity in certain areas.
Results from the studies reviewed showed that acupuncture could balance the dysregulated activity of certain AD-affected brain areas. A study by Shan[33] using both MCI and AD patients found the activity of different areas to be modulated in each. Regions activated in MCI was the left superior temporal gyrus, left cerebellum, right middle frontal gyrus, right inferior frontal gyrus, and the supramarginal gyrus, while for AD were the bilateral cerebellum, the right inferior frontal gyrus, and the right middle temporal gyrus among others. Deactivation occurred in left inferior parietal gyrus in MCI patients and in right cuneus, left putamen and others in AD patients. Another study in mild to moderate AD patients by Zhan,[99] found that the combination of a cluster of points with donepezil increased fALLF values in the right precuneus, the middle frontal gyrus, and superior temporal gyrus. FC analysis showed that treatment enhanced the disrupted connectivity between the right precuneus and the left precuneus, right superior temporal lobe and right superior occipital lobe, while this enhanced connectivity negatively correlated with the ADAS-cog scores of those patients. A third study by Zheng,[100] measuring the effects of a three minute stimulation on LV3 and LI4 managed to diminish increased activity in the right hippocampus, right inferior frontal gyrus, and the middle cingulate cortex, while increasing activity in the left postcentral gyrus. Like the previous study there were negative correlations found between AVLT scores and the hippocampus-left precentral gyrus connectivity.

4.2.2 Acupuncture Improved Cognitive Function In AD And MCI Patients

All of the studies used cognitive assessments to measure the degree of efficacy of the treatment. One study by Xia[101] reported a decrease in serum APP and $A\beta_{1-42}$ levels and improvement of the event related potential in AD patients, indicating that some of the results found in the animal studies did cross over to human subjects, while a second one by Yue[102] reported that EA combined with memantine produced an improvement which was superior to either treatment alone, in oxidative stress markers LPO and NO while increasing SOD and thus anti-oxidant defence in VaD patients.
A positive thing in those studies is four out of five performed follow-up assessments which can provide some insight into the duration of the treatment effect. A study in MCI patients found no significant difference in post-treatment and the 8 week follow-up MoCA and

MMSE scores, contrary to the sham group which also presented with a degree of improvement post-treatment but the follow-up scores were lower than those before treatment as found by Chen.[103] In patients with vascular cognitive impairment with no dementia the post-treatment results of EA compared to those of the 16 week follow up saw a one point drop in the MoCA and MMSE scores and compared to week 32 they were still one point above the pre-treatment scores but had severely declined Huang[104] observes. In patients with AD a 24 week follow-up, Feng[105] noted that MMSE scores showed that the acupuncture effect persisted but there was decline in several domains of the test. The study further showed that the scores of donepezil patients showed a similar trend on follow up but on different domains of the MMSE. The only study that reported an actual improvement of the follow up scores compared to the post-treatment scores was the one that combined acupuncture with memantine mentioned previously.

A 2022 controlled trial by Nakamura[106] showed that San Jiao acupuncture was successful in improving behavioural and psychological symptoms of dementia (BPSD) as measured by the Neuropsychiatric Index Questionnaire.

4.3 Critical Analysis Of Data

In order to evaluate the results of the pre-clinical studies reviewed, there must be some consideration of the characteristics of the animal models used. To date, an animal model that expresses the full spectrum of AD pathology has not been created. However, several models approximate one or many aspects, and some models present certain advantages when studying aspects of the pathology by expressing the said pathology in an exacerbated form. Thus, even if the results from animal studies provide an indication of what could work on human patients, these results should be taken with a grain of salt, although they do provide some insight into the potential mechanisms that apply in the cognitive improvement.

There are evidence of continued neurogenesis throughout the adult years of an individual's life, a fact which has received attention due to its potential role in the treatment of AD. In the brains of AD patients a number of immature neurons exist which suggests that neurogenesis persists in both aging and in AD, the number of these neurons correlating with a better cognitive performance in healthy adults.[107] Adult neurogenesis is required for the advanced functioning of the brain as well as for its contribution to synaptic plasticity,[108] processes which decline from the early stages of neurodegenerative diseases, AD included. Findings in post-mortem AD brains suggest that in the early stages neurons show signs of de-differentiation and return to a progenitor-like state, re-enter cell cycle, and ultimately become dysfunctional,[109] indicating that supporting neuronal differentiation and maturation could potentially slow the rate of progression. Several studies in this review reported an improved neuronal structure in the hippocampus and the cortex, with the most common findings being the orderly arrangement of neuronal cells, the repair of the nuclear cell membrane, along with the reduction of cell swelling. Further, in AD patients, S100β expression correlates with the number of dystrophic neurites indicating that treatment supported the neuro-restorative process.[110] This does indicate that some sort of improvement occurring in the cerebral environment, which is essential for neurogenesis and neuronal survival.[111] In that regard then, the most significant finding is the upregulation of the BDNF and its receptor TrkB in animal models, as BDNF/TrkB play a crucial role in the dendritic development of SVZ-derived neurons,[112] and while it is not the only neurotrophic factor influencing neurogenesis (as NGF is also very crucial to cholinergic neurons (it was found to be upregulated by acupuncture in an older study)).[113]

Mesenchymal stem cell (MSC) transplantation has been receiving interest as a treatment for Alzheimer's disease, however it has been observed that these cells have difficulty differentiating.[114] BDNF signalling is essential for presynaptic differentiation of excitatory and inhibitory neurons, and rat experiments, BDNF administration was shown to restore progenitor cell proliferation and promote neuronal differentiation [115] so the upregulation of BDNF might provide substantial support to this intervention. Exogenous BDNF administration is ridden with many challenges and obstacles, namely the crossing of the BBB and the invasiveness of surgical procedures, so acupuncture could potentially support both MSC transplantation by means of upregulating BDNF. In the same way acupuncture could potentially enhance the brain's innate neurogenic process starting from the earliest stages of AD where BDNF is dysregulated[116] and during its progression, where downstream BDNF signalling may provide other types of benefits, like supporting the cognitive functioning that deters with aging[117] since strategies to salvage hippocampal neurogenesis have not been without side-effects.[118] However, any intervention that aims to enhance neurogenesis must also simultaneously address neuroinflammation. The presence of pro-inflammatory cytokines can shift the proliferation and differentiation of neural stem cells towards astrocytes and oligodendrocytes instead of neurogenesis, as a study comparing post-mortem samples of AD patients showed an increase in astrocyte-like cells with progenitor characteristics in comparison to healthy samples.[119] Furthermore, pro-inflammatory cytokines like TNF-α, IL-6, and IL-18 are responsible for the inhibition of the differentiation and the death of progenitor cells.[120] In that regard acupuncture has shown that, at least in animal models, it can reduce pro-inflammatory cytokines and modulate key inflammatory pathways. A concern regarding this though, is that although acupuncture shows to have an effect on several pro-inflammatory processes and Aβ, APP, and BACE1 it does not seem to affect significantly plaque size and plaque load, the presence of whose favours the inflammatory state. Additionally, astrocytes in the neurovascular unit appear with swollen end feet which limits the ability of the BBB to remove Aβ[121] from the brain. It seems that acupuncture may be able to reduce inflammation and regulate inflammatory pathways but this effect seems to be stage-related, while even in the earliest stages, it cannot be characterized as a reversal. In a state where the pathology has advanced it might prove that acupuncture is unable to produce a substantial effect in the reduction of inflammation, although it may contribute together with the medication to slow the rate of the progression and sustain brain function on a certain level for a certain time. Healthy microglia and astrocytes, provide an invaluable support to the CNS but when activated, they contribute to a number of detrimental processes in AD, such as amyloid production, tau hyperphosphorylation, the dysregulation of the neurovascular unit, the loss of the integrity and function of the BBB, and the halting of adult neurogenesis. Switching the activation of astrocytes and microglial back to their supportive role or sustaining it, is a key crucial to the prevention of the disease and delaying its progress, as well as the success of any treatment that aims to regenerate nerves or restore their function, as BDNF coming from astrocytes and microglia is essential for the maintenance of learning-associated new dendritic spines,[122] which could be significant if cognitive rehabilitation is being implemented to the patient. However, since microglia are responsible for the phagocytosis of Aβ it seems rather difficult achieving a significant clearance of Aβ without being able to convert the microglial polarization in areas already present with severe plaque formation, although acupuncture might prove somewhat effective in delaying the rate of deposition, as was shown by its influence on amyloid related molecules.

The influence of acupuncture on inflammation may also have benefits related to the prevention of AD. Microglial activation and neuroinflammation cause synaptic dysfunction prior to neurodegeneration and memory impairment in AD.[123] The general hypothesis on

anti-inflammatory treatment in AD is that it should be implemented as a protective measure but while many types of immune or anti-inflammatory therapy have been successful in animal models, the same results did not appear on clinical trials, and on the contrary, these trial came with serious adverse effects.[124] Concerning inflammation then, it seems safe to say that acupuncture can provide support in any treatment that requires reduction of inflammation but as the data indicates it can be more effective as a preventive measure or in the very early stages of AD as a means to sustain the healthy activity of microglia and astrocytes.

The data also supports the idea that acupuncture may have significant neuroprotective effects, mainly through BDNF. BDNF also serves multiple other functions other than neurogenesis in the brain as it has a role in synaptic plasticity, LTP, memory formation, prevention of apoptosis and neuronal survival, synaptic strength and transmission, and antioxidant defence.[125] The activation of BDNF through its receptor TrkB is important to nerve protection as BDNF mainly regulates the survival of nerve cells and synaptic plasticity by triggering the BDNF/TrkB/PI3K/Akt signalling pathway. Downregulation of PI3K/Akt pathway specifically has a role in many AD-related pathological processes. GSK3-β, a downstream target of PI3K/Akt, induces Tau hyperphosphorylation and a reduction of NMDA receptor subunits NR2A/B.[126] It is reported that the shrinkage and destruction of dendritic spines is associated with NMDAR mediated LTD,[127] hence the upregulation of NMDA receptor subunits NR2A and NR2B and the downregulation of GSK3-β as was shown, may enhance the neuroprotective effect of acupuncture. The loss of dendritic spines in cortical pyramidal cells is considered a hallmark of the cognitive decline during aging, a process exponentially augmented in AD due to severe neuronal loss[128] and amyloid pathology.[129] The upregulation of BDNF/TrkB can help maintain the dendritic spines and impede spine pathology a fact which can be positive not only for AD patients, but also for aging people in general. Another downstream target of the PI3K/Akt is mTOR. The downregulation of PI3K/Akt through the upregulation of mTOR is considered an early event in AD pathogenesis, and has a role in enhancing Aβ generation and deposition, upregulates BACE1, contributes to p-Tau and enhances autophagy and the activation of mTOR is mediated through GSK3-β.[136] Activation of mTOR also downregulates p38MAPK, a MAPK involved in apoptosis,[130] neuroinflammation,[131] and tau hyperphosphorylation.[132]

In a neuronal cell culture, a PI3K inhibitor reduced the neuroprotective effect of nicotine.[133] Loss of nAChRs can lead to the dysfunction of the DMN, due to the fact that they are able to regulate its activity.[134] The studies reviewed showed that acupuncture can upregulate nAChR content and restore cholinergic activity, while being able to modulate the activity of several areas affected during the disease process in humans, including the DMN, which can prove beneficial during any stage of the disease as it can enhance synaptic function and help improve the symptoms of AD overall, since the maintenance of the integrity of the brain circuit and function are essential for the retaining hippocampus-dependent cognition.[135]

Another interesting finding is a significant increase in both synaptophysin and PSD-95 in the prefrontal cortex was recorded. PSD-95 is an important scaffold protein with multiple functions that eventually determine the synaptic response.[136] Susceptibility to glutamate-induced neurodegeneration is supposedly modulated by an altered neuronal expression of the PSD-MAGUKS family of proteins of which PSD-95 is a part of,[137] and its loss precedes both plaques and NFTs. It has been shown that the increased expression of PSD-95 could be neuroprotective, to a certain extent.[138] Similarly, synaptophysin is a pre-synaptic protein that regulates synaptic vesicle endocytosis, and regulates activity dependent synapse formation[139] which in decreased during the earliest stages of AD, to the extent of 43% in the

CA1 area,[140] while its loss is substantial in the frontal cortex of AD patients[141] and it is also influenced by NFTs[142] and by Aβ oligomers.

Although these findings are encouraging, neuronal dysfunction in AD occurs way before any clinical symptoms appear, and by the time of diagnosis we must consider that the disease has already progressed to some extent. The disease progression and its effects do not depend on the number of existing neurons but rather on their functionality, and how well they are preserved, which significantly impacts pathological progression.

The data here indicates that neuronal functioning is impacted by acupuncture, we cannot judge how impactful these modifications are even we assume that the same mechanisms working in the animal models are those working in the human brain. Animal models are unreliable to judge this, since mice and rats do not possess the late-maturing cortical regions and nerve cells that are affected in humans[143] so the questions arises of how these results translate to the human brain. In humans, a favourable modulation of functional connectivity did appear, which implies an enhanced synaptic activity, an event that may have multiple beneficial consequences that are worthy of investigation. Synaptic activity modulates Aβ in the brain.[144] The strengthening and maintenance of active synapses may come about through the release of neurotransmitters during neuronal activity,[145] and small amounts of Aβ may facilitate the presynaptic release of glutamate that contributes to neuronal excitotoxicity in low-activity rather than high-activity neurons. Additionally, for the cleavage of proBNF into mature BDNF, high frequency activity along with NMADRs are essential.[78] Further, the myelin sheath of the late maturing neurons that are affected in AD, produced and sustained by neuronal activity.[164] Another thing is that synaptogenesis is an activity dependent process.[146] In AD the functional connections of the brain might be different throughout the different disease stages. While functional connectivity changes are a characteristic of early AD, late AD is characterized by a decline of anatomical connectivity.[147] Since neuronal activity enhances neuronal survival, acupuncture may prove to be more impactful than simply improving cognitive function as the studies show. If the ability of acupuncture to improve synaptic structure and efficacy, neuronal structure, function and ultimately survival then that could make acupuncture an impactful treatment approach for AD in various disease stages, although this is something that needs to be verified by testing methods were not included in the studies reviewed here.

There is another potential benefit to the modulation of the functional connectivity by acupuncture. It is suggested that the decline of executive control in AD, is not related to the impairment of the frontal lobe but is rather due to the partial disconnect between the posterior and anterior cerebral areas.[148] Therefore, simultaneous activation of the cerebellar, temporal and frontal areas of the brain could rectify this event. AD patients also exhibit decreased activation of the default mode network (DMN), which can be a product of a low nAChR level as well as amyloid accumulation. Modulation of the activity in central areas of the DMN such as the precuneus, the inferior and middle frontal gyrus was observed and could contribute significantly to cognitive performance. From mild through to severe AD, there a gradual decline of FC between the posterior cingulate cortex (PCC) and other areas such as the inferior temporal cortex, hippocampus, and especially the mPFC and the precuneus/cuneus, although there was no mention of acupuncture influencing activity or connectivity of this area. Taking into account that amyloid plaques first appear in the neocortex,[149] acupuncture may prove helpful in rescuing synaptic function in the PFC and thus rescuing executive control, especially at the earliest stages of the pathology.

Another cause of neurodegeneration in the human brain in a chronic state of cerebral hypoperfusion, and has been well implicated in setting the stage for AD,[150] participating in the lowered energy metabolism, amyloid accumulation and tau hyperphosphorylation, generation of oxidative stress, as well as brain atrophy. Vascular dysfunction is prominent in

prodromal AD and reduced CBF is correlates with the rate of amyloid deposition.[151] Acupuncture has shown that it can improve CBF especially in the PFC, which may have potential implications on throughout disease progression. On the one hand improvement on the CBF of the prefrontal cortex is important, as the prefrontal cortex, especially the mPFC, serves memory and executive functions that are impaired both in aging and AD[152] and it's one of the earliest areas affected by AD, hence the protection of the hippocampus – PFC connection and the overall functionality of the prefrontal cortex can be of benefit at the stages where some of these neural connections have been able to survive. However, further research is required to clarify this effect in the human brain since the prefrontal cortex between rodents and humans presents with significant differences.[164] On the other hand, white matter loss is significantly correlated with the transition from MCI to AD,[153] but again this might not translate in the human brain and requires investigation.

Another event related to the development of AD and its pathological event is mitochondrial dysfunction and oxidative stress in the brain. Mitochondrial dysfunction and oxidative stress are considered early-transpiring events in AD as well as components of the aging brain,[154] so perhaps intervention at those points may have neuroprotective effects at those stages. As was observed, the reduction of NAA may prove of significance. NAA is a marker of the functional integrity of neuronal mitochondrial metabolism and may be critical for myelinogenesis,[155] since its breakdown product, acetate, partakes in the production of myelin lipids.[59] Increased oxidative stress is a product of mitochondrial dysfunction and may trigger or exacerbate neuroinflammation in aging and AD.

Bearing all of the above in mind, are we able to make a definite statement concerning the role of acupuncture in the treatment of Alzheimer's disease? There are some obstacles to this. Although through the animal studies a wide array of mechanisms was discovered that has the ability to affect several pathological processes, a conclusion based on those results cannot be made because of a) the role of certain processes and molecules participating in the disease process has not yet been clarified by research. Taking into account the complexity of AD, in the way that we cannot exclude their benefit, by the same way we cannot be 100% sure of their impact. This makes it somewhat challenging for acupuncture research to focus on a particular mechanism without knowing what that particular mechanism is. B) Although a large number of molecules were addressed here and some with key roles, these by no means represent the disease process as a whole. For example, the complement system has also been found to participate in AD pathology (ref), but no studies were found connecting acupuncture and the complement system. Taking these into account, and although from the TCM perspective acupuncture is a very precise treatment approach with clearly defined treatment principles and a variety of ways to address them, from the biomedical perspective it seems to have a wide-acting influence, which is both its advantage and disadvantage. The disadvantage is that since we cannot clarify precisely, due to the lack of understanding of its mechanisms, so we cannot implement like a drug in which the input-output relationship is relatively stable. However, it presents an advantage because due to its homeostatic ability it can address a variety of mechanisms that would normally require a combination of drugs as is indicated by the results reviewed here.

Another obstacle is assessing the effect of acupuncture in human AD patients is that besides imaging technology, or blood and serum testing, the evaluation of the therapeutic effect relied solely upon cognitive testing. There are some things to consider regarding the exclusive use of cognitive testing both in measuring outcomes and screening patients. Cognitive tests like the MMSE, MoCA, and the ADAS-Cog, which were extensively used here are not complete neuro-psychiatric examinations and even a single point difference in their scales might actually represent varying degrees of severity and improvement. Hence

their results cannot yield a definite diagnosis or give account to the mechanisms that underlie the patient's improvement.

The results however point towards a direction. Amyloid, tau, and neuroinflammation are three factors that form a feedback loop from the earliest stages of the disease[156] and the best way to halt the progression of either one is by addressing all three simultaneously. Given that acupuncture does not only address this factor, but also cerebral hypoperfusion, neurotransmitter dysfunction, connectivity issues, and mitochondrial dysfunction, makes it a viable candidate for further research on the prevention and treatment in pre-clinical and the earliest stages of AD. The fact that acupuncture modulates connectivity in certain cognition related areas may also make it applicable for later stages as well, although judging from the evidence gathered here it would be best if acupuncture supplements medication and other forms of therapy. For reasons mentioned previously like the lack of anatomical connectivity and the extensive neural damage that accompanies later stages, the data suggests that acupuncture may not be very impactful, other than it being a symptomatic treatment. A 2020 review[157] of studies conducted mostly in China, concluded that acupuncture (and acupressure) could potentially impact BPSD positively, remarking the lack of methodological quality. Indications remain positive that acupuncture can have an impact on later stages of the disease, improving the quality of life of both patients and caregivers.

Aging is the biggest risk factor for AD. There are also multiple other conditions that set the stage for the development of the pathological events that lead to AD. For example, people with PTSD tend to be more susceptible to dementia.[158] On the other hand, diabetes also increases the risk for dementia,[159] which indicates a variety of predisposing factors. Taking into account that there are evidence of cortical reorganization during aging, and that both Aβ and Tau have physiological roles in synaptic plasticity and neuronal functioning (ref), it wouldn't make it extreme to claim that in some people, due to pre-existing circumstances which favour the development of certain aspects of the AD pathology, AD eventually develops. The evidence presented here gives some credit to the fact that acupuncture may be able to support the transition to a healthy cognitive aging. Although research is advancing with great speed and technology affords us precious advantages, still the human brain is a very complex circuit with a very complex structure. Due to its ability to impact many processes, and that it is a safe and versatile procedure, acupuncture is a suitable candidate for investigation not only of its effects but also of efficient ways that we can implement its application.

4.4 Acupuncture Treatment of AD According To TCM

4.4.1 Foundations of Dementia In TCM

In TCM dementia is categorized under the term "lao nian chi dai" which roughly translates as senile feeble mindedness or senile psychosis. It does include forgetfulness as a symptom, but as a whole it refers to the totality of the neuropsychiatric symptoms manifested in dementia.

According to TCM, aging is characterized by the decline of the pre-heaven essence housed in the kidneys. This process is described in the Huang Di Nei Jing Su Wen (The Yellow Emperor's Classic of Internal Medicine – Simple Questions) (HDNJSW)[160] chap. 5:

"At the age of forty, the yin qi has decreased to half of its own [former amount]; one's daily activities weaken. At the age of fifty, the body feels heavy; the ears and the eyes are no longer clear. At the age of sixty, the yin [reaches a state of] limpness; the qi is severely weakened and the nine orifices are no [longer] freely passable. Below is depletion; above is repletion. Snivel and tears both flow." With aging as its biggest risk factor, dementia is a condition that begins with a deficiency of the pre-heaven essence and proceeds through stagnation to form a mixed condition of deficiency and excess, with the subsequent development of phlegm and blood stasis.

At the stage of memory loss, deficiency may be more pronounced. In the Yi Lin Gai Cuo (Correcting the Errors in the Forest of Medicine)[161] (Yi Lin Gai Cuo) it states that "in the aged who do not have memory, the brain marrow is gradually emptying." Deficiency of marrow, specifically in the brain, is the main cause for memory impairment. In the HDNSW it states that the "kidneys generate the bones and marrow" so the marrow is closely related to the state of the original qi of the kidneys. A 2022 study[162] amongst 121 patients with mild cognitive impairment (MCI) found that deficiency of marrow was the most prevalent syndrome, with turbid phlegm obstructing the orifices being second.

Equally important for the marrow is the ability of the spleen and stomach to transform the post-heaven qi. According to the Huang Di Nei Jing Ling Shu (The Yellow Emperor's Classic of Internal Medicine–Spiritual Axis) (HDNJLS),[163] "when the jin and ye liquids of the five types of grain find together, they will generate a paste. Internally [this paste] will seep into the hollow spaces in the bones and supplement the brain with bone marrow."

A deficiency of marrow however cannot account for the whole spectrum of symptoms. Per the HDNLS in patients with a deficiency in the sea of marrow "the brain revolves, and there are noises in the ears. The lower legs cramp and vision is dimmed. The eyes see nothing. [Patients] are relaxed and sleep peacefully." This is not always the case with many patients.

The exhaustion of pre-heaven essence will eventually result in stagnation and the production of phlegm and blood stasis, which may account for the symptoms not described in the HDNJLS. In the Jin Gui Yao Lue (Synopsis of Prescriptions of the Golden Chamber) (Jin Gui Yao Lue)[164] it describes this in the following way: "Channels and collaterals, nutrient essence, vital resistance and vital energy are all impaired. In such cases blood stasis will result." Blood stasis will then proceed to impair memory, cognition, and behaviour. In the Shang Han Lun-Discussion of Cold Damage,[165] clause 237 it reads: "when the patient is amnesic, there must be blood stasis." The Yi Lin Gai Cuo says about blood stasis: "The pathocondition of withdrawal and mania [manifests with] incessant crying and laughing, chiding, cursing, and singing regardless of who is present and much evil behaviour. [This is due] to qi and blood congealing and stagnating and the brain qi not connecting with visceral and bowel qi similar to dreaming." According to HDNJSW chap. 62 blood stasis affects mental functioning differently according to its location: "When the blood collects above and qi collects below, the heart is vexed and [the patient] tends to be angry. When the blood collects below and qi collects above, [patients] behave disorderly and tend to forget." The Su Wen Jing Zhu Jie Jie clarifies this point: "Blood is generated in the heart but stored in the liver. When blood is merged above, it must be exuberant (above) and qi must naturally be merged below, surging upward. Thus the heart and the liver are stirred, causing vexation, oppression, and irritability. If qi....is merged above this means the qi keeps on ascending and blood is naturally merged below. Above is separated from below, causing dissipated and scattered essence and spirit. As a result, there is derangement and forgetfulness." [166]

4.4.2 Pattern Differentiation In AD

The deficiency of brain marrow is the primary pathological basis for memory loss but it cannot account for the whole spectrum of symptoms appearing in patients with AD. The effect of aging in the visceral organs is mentioned in chap.52 of the HDNJLS: “At the age of fifty, the liver qi begins to weaken. The liver lobes are thinner. The gall liquid begins to decrease. The eyes begin to lose their good vision. At the age of sixty, the heart qi begin to weaken, as if they were affected by grief. Blood and qi slow down. Hence, one is incline to lie down. At the age of seventy the spleen qi are depleted. The skin is dry. At the age of eighty the lung qi weaken. The po soul departs. Hence one tends to make false claims. At the age of ninety, the kidney qi are burned up.” The decline of the kidney essence makes the liver, heart, and spleen, susceptible to the pathological changes which eventually manifest into the symptoms of dementia, and not only cause changes in the function of the organs but also result in the pathological formation of phlegm and blood stasis both as a whole and in the particular organs, hence the quote from the HDNJSW “When the blood collects above and qi collects below, the heart is vexed and [the patient] tends to be angry. When the blood collects below and qi collects above, [patients] behave disorderly and tend to forget.” In order to derive the possible patterns that may be encountered in AD patients, attention should be paid in the interactions of these three organs with each other since they can always the root or branch of the underlying symptoms.

4.4.2.1 The Liver

Since the liver and the kidney share the same source, the essence and blood, it would seem that this would be the first relationship to be affected. The decline of kidney yin would lead to a deficiency of liver blood and eventually liver yin, the subsequent qi stagnation would contribute to the consumption of liver yin which will lead to the upward rising of liver yang. Further, the inability of the liver to regulate the emotions may lead to the development of liver fire. On the other hand, kidney yang is the basis for the yang of the visceral organs that may affect liver qi and yang, leading to the loss of the liver’s ability to dredge the meridians. This would also lead to blood stasis and phlegm, something which can be augmented if the deficiency of kidney yang affects the transformation and transportation function of the spleen. The above conditions also favour the development of liver wind.

Besides the kidney, the spleen and the heart are closely influenced by the liver organ pathology. A deficiency of blood in the heart and liver will result in the failure of the heart and liver to regulate the emotions, while the stagnation of liver qi will undoubtedly affect the qi dynamic and cause a stagnation in the heart as well as the spleen, favouring the accumulation of damp and phlegm. Further, the depression of liver qi will impair the ability to regulate the emotions and that may turn to liver fire which may transmit to the heart. If the kidney yang deficiency has affected the heart yang, then this together with the stagnation of liver qi sets the foundation for the formation of phlegm, blood stasis in the heart, and the eventually combination with fire.

4.4.2.2 The Heart

The heart is affected by the decline of kidney essence as well. The imbalance of yin and yang in the heart will appear either as a disharmony between the heart and the kidney where the kidney yin fails to nourish the heart and would cause heart yang to flow upwards and

harass the spirit, as well as the inability for qi to descend downwards leading to accumulation of turbidity. Kidney yang deficiency would lead to inability of the heart qi and yang to move blood, resulting in poor nourishment of the orifices, and eventually obstruction by phlegm and blood stasis. The resulting qi stagnation, phlegm and blood stasis would lead to the consumption of the heart yin by fire and the combination of fire, phlegm and blood stasis would further harass the shen of the heart and obstruct the nourishment of it.

If kidney yang primarily affects the ability of the spleen to make blood this could also lead to a dual deficiency of the heart and spleen which will affect mental function by the lack of nourishment to the brain.

4.4.2.3 The Spleen

Since the root for the yang of the spleen is kidney yang, the deficiency would result in an overall deficiency of qi and blood that would also affect the heart and the liver. The decline in the transformation and transportation of the spleen would also result in the formation of phlegm which this time would not appear on the upper jiao but rather the middle and the lower. The formation of phlegm if it is found in the meridians could combine with liver wind if the liver is also affected and lead to the rising of wind phlegm,[167] which can block the orifices leading to dizziness and to seizure activity as this is observed in some AD patients. Another important aspect of this interaction is that if the spleen is unable to transform then this will also affect the production of marrow.

4.4.3 Pattern Differentiation In Literature

4.4.3.1 Patterns of Cognitive Impairment

Amongst 121 MCI patients in China, the predominant patterns observed were (in descending order), kidney deficiency and marrow reduction (34.71%), turbid phlegm obstructing the orifices (29.75%), deficiency of heart and spleen (14.88%), qi stagnation and blood stasis (10.74%), yin deficiency of the heart and liver (9.92%).[168] A cross-sectional study on 803 patients with vascular cognitive impairment observed 8 predominant syndromes: Qi deficiency, Qi stagnation, Blood deficiency, Blood stasis, Phlegm-Damp, Fire-Heat, Yang deficiency, and Yin deficiency, with 38% of patients being diagnosed with Yang deficiency.[169] The aim of the study was to further find the determinant symptoms for each pattern as well as which of these symptoms have the highest probability. For Blood deficiency they were blurred vision, dry eyes, palpitations, and insomnia indicating the liver and the heart as the main organs. For Blood stasis they were purple or dark lips, dim complexion, and blackish lower eyelid, tongue with ecchymosis and a dark tongue. For Qi deficiency they were chest oppression, sore waist and knees and palpitations were most probable followed by lack of strength, shortness of breath, lassitude of the limbs and body, and urinary incontinence suggesting the involvement of the heart, spleen, and kidney. Qi stagnation had chest oppression, sighing, hypochondriac pain and distention, and abdominal distention as its most dominant symptoms indicating that the heart and liver were affected the most. Results on Fire-Heat showed that dry stools, constipation, and desire for cold

drinks were the most frequent symptoms with agitation, irritability, insomnia, foul odour of the mouth, nausea, stomach burns, and aphtha of the mouth following. On Phlegm-Damp a greasy tongue and a slippery pulse were key determinants with dizziness, and headache following. The authors distinguished between two categories of yin deficiency. Those characterized by insufficient nourishment of the visceral organs were characterized by sore waist or knees, blurred vision, dry eyes, and high-pitched tinnitus, while those characterized by the inability of yin to restrain yang were characterized by insomnia, dreamfulness, palpitations, and expectoration. The researchers also sought symptoms that differentiate between the two categories and found that a deep-red tongue in contrast with a dry tongue and a rapid pulse are the best determinants. For Yang deficiency, sore waist and knees, blackish lower eyelids, frequent nocturnal urination, and dim complexion were noted as the key determinants. As far as differentiating between kidney yin and kidney yang the presence or not of cold symptoms such as aversion to cold, cold limbs, together with a pale tongue were the best differentiators as found by an analysis on 2765 cases of patients with kidney deficiency syndrome.[170]

4.4.3.2 Patterns of AD

The Word Federation of Chinese Medicine Societies reached a consensus in 2021 where the main clinical patterns for AD were determined.[171] These were: syndrome of marrow deficiency, spleen-kidney yang syndrome, liver-kidney yin syndrome, syndrome of yin deficiency and effulgent fire. A review of 200 articles between 2012-13 found a total of 12 patterns mentioned in literature, with the major ones being kidney essence decline with deficiency of marrow, representing 38.5 % of the cases, phlegm and blood stasis obstructing the orifices, qi stagnation and blood stasis, liver-kidney deficiency, and phlegm blocking the orifices.[172] Besides the pattern classification, it is worth noting that in this review the term intertwinement was used to describe the presence of phlegm and blood stasis in a pattern, which underlines their common presence in AD due to their mutual generation. Concerning phlegm and blood stasis, reports from contemporary physicians both take phlegm and blood stasis as the pathological basis of dementia,[173, 174]and since they mutually engender each other they should be addressed simultaneously. When they are found in the brain, clearing the brain collaterals should be the guiding principle. Two experienced physicians in the treatment of vascular dementia, professors Zhang Qing-Ping[175] and Jun Li,[176] agree that both phlegm and blood stasis should be addressed simultaneously, both agreeing that the clearing of the brain collaterals should be a part of the treatment strategy concerning phlegm and blood stasis. Considering that, pattern differentiation between AD and VaD is not so different, the above principles may also apply. An article by Zhang[177] described the main patterns of VaD as kidney qi and marrow deficiency, liver and kidney yin deficiency with decline of essence and marrow, spleen and kidney deficiency with damage of essence and marrow exhaustion, heart and liver fire hyperactivity, and accumulation of damp with phlegm obstructing the orifice, while a study among 63 VaD patients 27% belonged kidney essence deficiency, 25% to phlegm obstructing the orifices, 19% to liver-yang rising, 13% to qi and blood deficiency, 8% to fu-organ turbidity retention, 6% obstruction of the collaterals due to blood stasis, and 2% to hyperactive fire.[178] VaD and AD are very similar and contain each other in both TCM and modern medicine, so their patterns correlate as it is evident.

Concerning the pattern differentiation of BPSDs a review of 10 studies also found similar patterns revolving around the deficiencies of the liver, spleen, kidney, and heart combining with each other, complicated with blood stasis, phlegm, and fire which were more present compared to the previous studies.[179] As per the HDNJSW chap.74 "Symptoms of disorientation, confusion, convulsions and seizures, pain, and itching are usually due to fire and related to the heart"

4.4.4 Acupuncture Point Selection For AD

4.4.4.1 Principles Governing Point Selection

According to the HDNJSW there are four channels that link directly to the brain, the governor vessel, the foot yangming stomach channel, the foot taiyang bladder channel, and the yin and yang motility vessels. [180] Specifically for the marrow, the Yi Lin Gai Cuo says: "The clear [part] of the essence juice transforms into marrow and moves upward through the spine into the brain. It is called the brain marrow" However, to address the decline of original qi the conception vessel can also be employed according to the Qi Jing Ba Mai-An Exposition on the Eight Extraordinary Vessels[181] which states: "The two vessels of the ren and du in medical texts, are where the primal qi is engendered." The governor vessel might be important for the ascent of marrow to the brain, especially the points on the scalp, but the conception vessel may also play a part in restoring the production of marrow in the zang-fu and addressing their insufficient nourishment in cases of deficiency. For example, Zhongwan RN12 is the meeting point of the stomach, small intestine, and san jiao channels which are closely related to the post-heaven essence through the small intestine channel, the original qi through the san jiao channel, and the brain through the stomach channel.

What should also be considered is that dementia is a disease that involves the separation and disharmony of yin and yang. In the Zhen Jiu Jia Yi Jing [The ABC of Acupuncture] (ZJJYJ), book 1, chap.13 it writes: "When yin and yang are not in harmony, humor overflows and flows downward to the yin. The marrow and humor may both be diminished and descend, and if (the marrow and the humor) descends excessively vacuity ensues." It also states in book 1, chap.4 that: "Evils within the viscera leads to a disharmony of the yin vessels. When there is a disharmony within the yin vessels, the blood becomes lodged. If the blood becomes lodged, this leads to an exuberance of yin qi. If there is too great an exuberance of yin qi, the yang qi cannot fulfil its functions. This is referred to as a (condition of) barricade. If there is too great an exuberance of yang qi, then the yin qi will be unable to flourish. This is called separation. If there is exuberance of both yin and yang, neither may be able to fulfil is function. This is called barricade and separation." So in the case of organ involvement attention should be paid to the qi dynamic and to restore the normal flow between yin and yang by incorporating points that restore the qi flow (e.g. Siguan) or points that move open the brain collaterals like GB20, and GV16.

The other reason to facilitate movement though the meridians comes from the HDNJLS ch.18 in which it is written that: "In old [persons] the qi and the blood are weak. Their muscles and their flesh wither and the paths of their qi are rough. The qi of the five long-term depots strike at each other……Hence they are not of a clear [mind] during daytime, and they do not close their eyes at night." The hardening of the pathways of qi, or the blood vessels in modern medical terms, which implies impaired movement through the meridians

and eventually stagnation is already a component of aging. Further, promoting sleep when necessary can be of vital importance according to both the TCM and modern medicine perspective. The production of melatonin during sleep has several benefits for the protection against AD and AD patients such as improving synaptic plasticity and hippocampal neurogenesis, inhibition of Aβ deposition and tau hyperphosphorylation, increase of amyloid clearance through the glymphatic system, has anti-inflammatory properties, provides anti-oxidant defence, and overall improves cognitive function.[182] A study on the effects of acupuncture on the sleep quality of dementia patients, used many of the points that were common in the treatment of AD (GV20, HN9, HN3, HT7, ST36, and SP6).[183] Since no pattern differentiation was included in this study, points specifically addressing the underlying pattern of the disturbed sleep might prove beneficial to the patients.

4.4.4.2 Common Points Found In Literature

Three analyses on the frequency of acupuncture points were discovered and all exclusively relied on human trials. Two of them also accounted for the frequency of meridian usage.

In the analysis by Dong[184] the meridians used more frequently were the governor vessel, foot yangming, and foot shaoyang channels, while Yu[185] discovered that the bladder meridian also followed the previous order. Although no reference of the foot shaoyang going to the brain was found, its high frequency was related to the use of GB20 as a point of the yang motility vessel, GB13 as a point of the yang linking vessel, and GB39 as the gathering point of marrow. Findings on point frequency followed the same path. Dong found that GV20, ST36, HN1 Sichencong, KD3, SP6 Sanyinjiao, and PC6 Neiguan were the most frequent. Yu found that GV20, EX-HN1, HT7, ST36, PC6, and GB20 were the most frequent, while Wang[186] found ST36, EX-HN1, GV20, SP6, PC6, and GV24. While point frequency was different between the three analyses the points are very similar. When looking further down the list of points reported, there are some differences in the point frequency compared to this review, e.g. GV14 was no.12 in our list with about 3% usage but was found somewhat higher in these reports, something which could be attributed to the fact that animal studies were more predominant in this review and these studies tended to focus on acupoints on the head. Association analysis was similar between these two of these reports, where in one GV20 was frequently associated with HN1, PC6, SP6 while in the other GV20 was associated with EX-HN1, and PC6. The third report however found the basic combinations involved SP6, HT7, and BL10. Slightly different but similar points were found in a data mining analysis for vascular dementia.[187] In that report, GV20, HN1, GV24, GV26, and ST36, were the most frequently used points, while the top five combinations were comprised of GV20 combining with the other points on the top of the list (GV20 and HN1, GV20 and GB20, GV20 and GV26, GV20 and GV24, GV20 and ST36).

Professor Zhang Qing-Ping's input,[188] although it concerns vascular dementia, gives very useful clues for approaching point selection. His therapeutic approach is focused on the brain and is guided by "tonification coming the top priority, followed by dredging collaterals." Towards this aim, he employs the following points as the main points: include GV20, GV24, EX-HN 3, GV26, Chengjiang CV24, Fengfu GV16, GB20, Dazhui GV14, and Gongxue (Extra, 1.5 cun below GB20, level with the lower lip), combined with the body acupoints Xuanzhong GB39, KD3, ST40, ST36, SP6, PC6, and LI4. For tonification he combine GB39 with KD3 for the brain, marrow, and kidney, ST36 with SP6 to tonify blood, strengthen the spleen and nourish the spirit, GV20, GV16, GV14, to dredge the brain collaterals combined with ST40 to resolve phlegm, while to restore the normal flow of qi of

the whole body, he uses PC6, GV24, EX-HN3. It is also interesting that Dr. Zhang uses GV26 together with CV24 (the needle method on GV26 being the same as previously described) to reconcile yin and yang, a recurrent theme in the pathogenesis of dementia.

4.4.5 Studies On The Actions Of Acupuncture Points For AD

The action of several body points found in this review has been investigated from a biomedical perspective. KD3 was found to activate several cognitive related areas in MCI patients, like the middle frontal gyrus, the inferior and superior frontal gyrus, the cuneus and others.[188] In mild to moderate AD patients, EA at HT7, ST36, ST40, and KD3 were chosen according to the principle of tonifying the kidney and spleen, move phlegm, and awaken the shen in an fMRI study and resulted in the activation of areas of the limbic lobe, right hippocampal gyrus, left hippocampus, together with the medial temporal gyrus, areas that are affected throughout the disease progression.[189] In D-galactose injected rats, HT7 was found to upregulate the glucose metabolism of the hippocampus, thalamus, hypothalamus, frontal lobe, and temporal lobe.[190] PC6 is another point frequently used to calm the mind, and in a rat model of chronic mild-stress induced memory loss, it restored AChE activity,[191] while a study amongst migraine patients found PC6 to have vasodilating effects in the middle cerebral artery, while LV3 was found to increase cerebral blood flow.[192] ST36 has been investigated on its effects in neurogenesis with a number of studies observing a positive effect on cell proliferation, BDNF, and neuroblast differentiation in animal models,[193] and in this review it was used in 23.9% of the studies. ST36 and LI11 are the He-sea points of the yangming meridian, and in MCAO rats they were found to reduce reactive astrocyte proliferation.[194] In MCAO rats GB12[195] (a meeting point of the gallbladder and bladder channels) improved hippocampal neuronal morphology and decreased pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. SJ5 regulated pro-apoptotic factor Bcl-2 in the healthy rat cerebellum.[196] A study on eighty patients with acute cerebral infraction diagnosed with qi deficiency and blood stasis found that needling GB39 through to SP6 together with GV20, PC6, KD3, GV26, LI11, and CV23, observed various improvements in almost 90% of the patients.[197] Another study using EA at GB39 with HT5 observed increased activity in the frontal lobe, temporal lobe, parietal lobe, and the limbic system in patients with aphasia,[198] areas critical to AD. In 243 patients with cerebrovascular disease, Kim[199] sought to investigate the difference in cerebral hemodynamic changes between foot shaoyang and foot taiyang points on the head and legs. The effect of points on the head was greater than those on the legs for both meridians and according to the point location the cerebral artery that was in closer proximity was affected. For the foot shaoyang meridian, GB20 was found to affect the most hemodynamic indexes, while for the foot taiyang meridian it was BL3 Meichong and BL10. Other points of significance found in this study were in descending order of influence GB14 Yangbai, GB16 Muchuang, and GB34 Yanglingquan for the foot shaoyang meridian and BL64 Jinggu and BL40 Weizhong for the foot taiyang meridian.

An fMRI study of the cerebral changes in healthy young adults after EA at CV4 and CV12 observed a modulation of limbic-prefrontal connectivity by both of these points with areas of enhanced connectivity being the medial portion of the inferior frontal lobe and the anteroinferior portion of the anterior cingulate cortex, the hippocampus, parahippocampus, and the orbital gyrus.[200] A post 10-min. scan showed that the effect persisted with the only difference being that CV4 had slightly increased local connectivity in the hypothalamus while CV12 did so for the amygdala. A comparative study on the effects of adding GV20,

GV26 and HT7 to points on the body in VaD patients with hemiplegia yielded interesting results reflected in cognitive tests, cerebral glucose metabolism, and cerebral blood flow. Each point affected changes in different aspects of the MMSE, ADL, and FAQ. Adding GV20 affected the medial temporal lobe system, the diencephalon system and the prefrontal lobe, adding GV26 affected the prefrontal cortex, while adding HT7 affected the same regions with GV20 with the addition of the prefrontal cortical lobe but its effects was smaller than GV20. These changes were also reflected on different compartments of the MMSE, ADL, and FAQ. When all these points were added together their effect was found to be cumulative.[201]

4.4.6 Does Research Support Pattern Differentiation?

Most of the animal studies reviewed included on around three points on average which were mostly on the head. Studies with human subjects used a higher number of points but none of these studies included TCM syndrome differentiation. Since it is a significant aspect of acupuncture treatment, the question arises: is there room for syndrome differentiation? A study comparing patients that received treatment according to syndrome differentiation and patients who did not, found that the cognitive improvement was identical between the two groups of patients but the group who was treated according to syndrome differentiation experience relief in other complaints.[202] There were some novel acupuncture methods that were found to be successful in achieving results. For example, San Jiao acupuncture (which includes CV6, CV12, CV17, ST36, and SP10) is recommended by the Word Federation of Chinese Medicine Societies guidelines for the prevention and treatment of AD, and is based on the principle of fostering the original qi, regulating qi and harmonizing blood. Since it includes only points on the body, it may very well benefit from the addition of other points either on the head or body, like GV20 which combined with ST36 in a significant proportion of the studies. Further, the statistical analysis supports the integration of successful points combinations with points according to syndrome differentiation, as in the use of GV20 with GV24 which was researched as a pair in 5 studies, but both points were found present in 11 studies in total. Therefore it seems safe to assume that the combinations found here can be expanded and adjusted according to the treatment principles, the needs of the patient, and the judgement of the practitioner without affecting treatment outcomes.

4.4.7 Components of a treatment regime

4.4.7.1 Duration Of Treatment

Most of the studies on human patients had a treatment frequency of 3 times per week, and the shortest duration of treatment was 6 weeks. The average duration of treatment for human studies was 9 weeks. The shortest duration for those studies using EA was 8 weeks. The longest follow up examination showing no severe decline was 16 weeks, which registered a 1.5 point drop in the MMSE.

Persistence of improvement with significant decline was marked at 24 weeks. In the one remaining study patients were treated daily. If we take the 16 week mark as the maximum length of time that patients receive acupuncture treatment, then that could indicate that after a certain treatment cycles, less treatments could be necessary to maintain or improve the

effects in cognitive performance, which can potentially reduce the costs of treatment forthe patient since acupuncture is not a part of intramural care and too many treatments will carry potentially serious costs. The exact cycle duration and treatment break times should be precisely investigated, however it seems there is space for flexibility, between 6 to 8 weeks of treatments and a space between 16-24 weeks maximum as a break.

Considering that AD affects mostly elderly patients, treatment three times per week may improve challenging in an extramural setting. Perhaps a treatment twice or once per week may achieve results over a longer time period but this still needs to be verified by treatment. The fact that all the human studies reviewed here were conducted in China where acupuncture has much greater acceptance from patients, could augment patient compliance, but this might not hold true for many western patients. Although it might be challenging to begin such a rigorous treatment regime, a duration of 6-8 weeks might be tolerable to some patients, especially once improvements start being noticeable and start to positively affect their quality of life. On the other hand, a break of 16-24 is quite long and may permit for less frequent visits to sustain the results, especially if herbal medicine is prescribed to sustain the effects during treatment breaks. Being as it is, we are forced to draw conclusions from the data available and those indicate that the minimum duration and frequency of treatment should be 3 times per week for 6 week, with a 16 week break between treatments and an average needle retention time of approximately 30 min.

4.4.7.2 Stimulation Parameters

69% of the total studies included here used EA, while from the ones who didn't, only a handful did not employ needle manipulations. There were two animal studies comparing the effects of different frequencies of EA and both found that higher frequencies resulted in an enhanced therapeutic outcome, a finding consistent with another review on this subject.[170] In animal studies either a direct low, high, or alternating frequency was used. In human studies three studies used an alternating frequency (one used a 2/50 Hz wave, and two used a 10/50 Hz wave, one used a 2.5 Hz wave exclusively, another a 3 to 15Hz wave, and the remaining three used manual stimulation, so a conclusion on the effects of high frequency EA on human patients cannot be drawn. As far as the current intensity of EA, in all cases it was adjusted to the patients' tolerance. Since all stimulation methods achieved results, the decision on what method to use and with which parameters remains on the guiding principles of treatment and the acceptance of the patient, in the case of EA.

Regarding manual stimulation, the even, reinforcing, and reducing stimulation were all found throughout the studies. The twirling manipulation was used more often than lifting and thrusting, with the duration of the manipulation lasting between 30s to 2 min. with an interval between them that varied throughout. Some acupuncture methods like the San Jiao method have set directions for the stimulation of each point, but like EA, stimulation parameters are dictated by the guiding principles of treatment. The needling depth was also varied between the human studies with studies that including the needling depth, presenting a variation from 15mm to 3 cm and of the needling size between 0.2 to 0.35 mm.

4.4.8 Can acupuncture alone treat AD?

According to the HDNJSW chap.3 “the source and preservation of the Yin come from the five flavours of food in the diet” while in the ZJJYJ book 6 chap.7 it says “insufficient form should be warmed with qi, and insufficient essence supplemented with flavour.”

Since the kidney essence is the source of both transformation and generation of yin and yang, the above statements indicate that the herbal medicine should considered for the treatment of AD, especially for the supplementation of marrow and of the various organs’ yin deficiencies. The study by Shi[111] also noted an insignificant improvement of VaD symptoms in patients with kidney-essence deficiency, while the opposite held true for the liver-yang rising and the phlegm obstructing the orifices syndromes. Herbal medicine has long been used in TCM to treat the symptoms of dementia, and various prescriptions, single herbs and their active compounds have been and are currently being investigated for their contribution in the fight against dementia, with many of them presenting significant improvements of the various pathomechanisms involved[203,204] making herbal medicine something to be considered, if not being essential, with numerous herbal medicine prescriptions addressing the pathophysiological mechanisms of AD successfully.[205]

Besides herbal medicine, these statements from the classics suggest that diet modification can improve the treatment outcomes. It is becoming increasingly clear that the gut-brain axis plays a role in many diseases and AD is one of them, with changes in the gut microbiota affecting the neurotransmitter level in the brain via the stimulation of the vagal afferent fibers.[206] Additionally, the presence of amyloid proteins in the gut can make the brain more sensitive to amyloid accumulation and lowers the inflammatory threshold.[207] High levels of inflammatory cytokines produced by gut microbiota can reach the brain through a disrupted blood-brain barrier (which is another characteristic of both aging and neurodegenerative diseases)[208] and trigger neuroinflammation by activating microglia and astrocytes.[209] Current evidence agrees with the TCM dietary principle of avoiding phlegm producing foods and suggest the avoidance of whole-fat dairy products, which increase the risk for cognitive decline in the elderly,[210] and promotes the consumption of anti-oxidant and anti-inflammatory foods.[211]

Exercise therapy is also another important aspect of AD treatment and prevention. A 2-year intervention of diet, exercise, and cognitive training produced a remarkable sustained effect in the cognitive performance of elderly at risk of dementia.[212] A sustained and prolonged exercise routine can increase the levels of BDNF in the brain, especially high-intensity,[213] although its effects are shown to be sex-dependent and may require further investigation.[214] For exercise to assert its effects on BDNF a continuous program is required, and that could present a challenge to the aged population, especially when it is of high-intensity. However, since mild exercise also produces effects, being consistent seems to be of greater importance. Tai ji and qi gong are exercises that are moderate in intensity, and their execution requires coordination. An RCT among elderly people without dementia noted that subjects who participated Tai ji exercise and those who engaged in social interaction not only improved neuropsychological scores but also presented with increases in brain volume.[215] In another RCT, 1-year five-animal qi gong training program of about 45 min. duration for 2 days a week or more in elderly at risk of cognitive decline, improved their MoCA scores and was evaluated to lower their risk of cognitive decline.[216] A systematic review on the effects of Baduanjin on middle-aged and elderly adults concluded that it can be effective in improving their global cognitive function.[217] In the HDNJSW chap.59 it is stated that: “the joints of the bones are the places where the hollow space in the bones is filled and from where the brain marrow is augmented” and both Tai ji and qi gong adhere to this principles. But patients should not only be limited those. For example, a dancing program in elderly adults improved increased the grey matter more than a traditional exercise regime.[199] We can say that any movement is better than no movement.

The effect of social interaction is something that cannot be overlooked when referring to AD. The neurological implications of the disease may confer a number of mood disorders in AD. Even in persons with MCI, the fact that they may suffer some symptoms might produce isolation with detrimental effects on the patients' psychological state, thus worsening the prognosis. Social interaction has been found to have positive effects in animal models regarding spatial memory,[218] and neuroplasticity[219] among others, thus making the cerebral environment more susceptible to the positive changes that any treatment may provoke.

4.4.9 Possible Directions of Acupuncture Research

The data collected here indicate that acupuncture may prove efficient in preventing AD delaying its pathological progression, alleviate its symptoms, and reduce the conversion from MCI to AD. An issue that most of the studies present is their short duration although most of the human studies have, rightly so, included follow-up assessments.

From the data of the animal studies, acupuncture has shown to exert its maximum effect from the earliest stages of the disease. A meta-analysis of cohort studies of MCI patients showed that the rate of conversion to dementia is less than 50%, but annually it averages around 7%.[220] That being the case, in a 5 or 10 year longitudinal study, could acupuncture improve these outcomes, and using which parameters? The figures from this meta-analysis suggest that MCI, although a prodromal state, does not guarantee the progression to AD. The issue in researching the prevention of AD is that there is no definite understanding of the pathological mechanisms of AD. Apart from genetic factors, the risk factors for AD are many making it difficult to assess acupuncture's impact on the prevention of AD, and MCI although not a definite factor, provides a direct relationship that allows us to do so.

Besides the interventions that could be benefitted by acupuncture like neurogenesis, MSC transplantation, and anti-inflammatory treatment, another area worthy of research is the long-term effects of the simultaneous treatment of acupuncture combined with AD medications. In one study here the combination proved superior to either treatment alone, so it is worth examining if these interventions can enhance each other in the long-term with the potential benefits for the patients being the avoidance of the adverse effects of medications, and the improvement of the costs of acupuncture treatment. A study like this involves many parameters like medication dosage and treatment duration, so it might prove more practical to solidify the parameters of acupuncture treatment like the duration of treatment required for the effects of acupuncture to take place and the interval between acupuncture treatment cycles. Then an assessment should be done comparing different medication dosages during the treatment periods and their effects on cognitive performance, as well as a comparison between no acupuncture and no medication. Such a study would require a large number of patients that comply over a certain period of time and time and resources from the practitioners involved, so the practicality of such a study is beyond the reviewer's expertise to assess. This type of study in AD patients might further complicated by the condition of patients, especially those with BPSDs so it might prove easier to perform it on patients with mild AD, than those in the later stages.

5. Concluding remarks

5.1 Would Acupuncture Work?

Whether or not acupuncture works has been a long-lasting debate. While it is true that perception influences results as it is demonstrated by this[221] and other studies, observations during this review provided some insight into this question.

In the study by Chen[137] acupuncture at both real and sham points resulted in an improvement in MMSE scores. Although that seemed surprising at first, the regression of MMSE scores back to pre-treatment levels of the patients that received sham-acupuncture indicates that the results were not due to the placebo effect. Another consistent finding in several studies was that the improvement of neuronal morphology in different brain areas was present in both sham and real acupuncture groups. Perhaps this was due to the response to the acupuncture sensation, however differences were observed in the magnitude of improvement, the extent of the area involved and that there were differences between sham and real acupuncture in the markers involved in each study. Another observation is the great difference in the modulation of activity between sham and real acupoints. Needling real points yielded in a much more cohesive and extensive brain activation than the needling of sham points in human patients.

While it the exact mechanisms of acupuncture are yet to be elucidated, something which is difficult to do without extensive knowledge of the mechanisms of the human body itself, ample evidence was found here in support of the fact that acupuncture has distinct effects, and that those are point-specific, and while they do not confirm its efficacy, they do confirm the validity of its effect.

5.2 Limitations Of This Review

One limitation of this review the small amount of studies found. 44 studies is a very small amount to reach any definite conclusions despite the fact that many pathological mechanisms implicated in AD were addressed by them. The number of human studies was also exceptionally low highlighting the need for more studies if a definite conclusion should be drawn regarding the point usage and the treatment parameters. Unfortunately, the lack of proficiency in the Chinese language led to the exclusion of a vast number of studies performed in China therefore limiting access to studies that included syndrome differentiation and potentially multiple approaches to treatment.

5.3 Epilogue

Acupuncture has been proven safe and effective in improving the cognitive function of AD patients from the earliest stage onward. This review summarized some important pathological aspects that acupuncture can improve such as neuronal plasticity, neurogenesis, neuroinflammation, synaptic transmission, cerebral blood flow, oxidative stress, and glucose metabolism in animals. The presentation of the findings of this review attempted to consolidate the value and need for further research in the effects of acupuncture for AD, both as a stand-alone treatment and as a complementary therapy to assist other types of interventions. It has further attempted to provide some information on the parameters of treatment that would constitute a successful acupuncture treatment regime. With no medication being yet successful in changing the pathological course of the disease, the need for efficacious, non-invasive treatments is still present and according to the findings

presented here, acupuncture could be a serious candidate for that role. Only in the Netherlands there are currently about 280.000 people currently living with dementia, with this number reaching 420.000 by 2030 and nearly doubling at 520.000 by 2050. Dementia care also places a huge economic burden on the health care system which is expected to reach 15.6 billion euros by 2030,[3] ranking dementia as the 3rd place in healthcare costs in the country. It then becomes important for the patients, that the effect of treatment methods improving their condition is consolidated by research and integrated into the healthcare system so that less pressure in put on the patients, their caregivers, and the healthcare system overall.

Although most studies in this review are pre-clinical, the few clinical evidence presented here together with those from the animal studies suggest that there are potential benefits to reap by continuing the research on acupuncture in AD, maybe not as the sole method, but as a complementary therapy or an adjuvant therapy to improve the performance of other approaches. Acupuncture, with its versatility and its wide range of applicability holds promise that it can carry a proportion of this weight however further research is necessary to clarify the efficacy, mechanisms, and the specifics of a successful integration in the treatment of patients with AD.

Furthermore, the combinations and treatment strategies found here can be included in the treatment of the elderly, as they can be an ally to the reorganization of the aging brain. The TCM principles outlined here concern both the aging process and AD and can be taken into consideration in general when dealing with the aging population.

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[1] https://www.who.int/news-room/fact-sheets/detail/dementia

[2] https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

[3] 'National Dementia Strategy 2021 - 2030', n.d., 4.

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