

Theoretical Analysis on Standardization of Time-Based Moxibustion with Linggui Bafa for Intervention in Mild Cognitive Impairment: From the Perspectives of Time-Based Qi Transformation and Meridian Time Sequence

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Abstract: Mild Cognitive Impairment (MCI) is the only reversible intervention stage of Alzheimer's Disease, with a high prevalence and disease conversion rate among the elderly population in China. Western medical interventions can only delay cognitive decline in the short term, and are difficult to repair the disorder of central circadian rhythm, with limitations in efficacy and medication safety issues. Time-based moxibustion with Linggui Bafa fits the core pathogenesis of MCI characterized by deficiency in origin, excess in superficiality, and time sequence imbalance, and has outstanding advantages in time-selective intervention. However, the current research in this field faces problems such as fragmented theoretical system, inconsistent intervention standards, and large research heterogeneity, which restrict its standardized and evidence-based application.

This study adopts methods of literature research, interdisciplinary coupling and standardized system construction, integrates the core theories of time-based qi transformation, extraordinary vessel time sequence and Linggui Bafa, constructs a four-dimensional theoretical framework of "celestial time qi transformation - meridian time sequence - moxibustion stimulation - brain cognitive repair", identifies three core syndrome types of time-based qi transformation imbalance in MCI, and elucidates the mechanism of time-based moxibustion in improving circadian cognitive impairment by regulating central circadian clock rhythm, repairing hippocampal neuroplasticity, and balancing time-sequenced inflammation.

Meanwhile, this study establishes a standardized intervention system integrating time-sequenced syndrome differentiation, time-selective acupoint selection, quantitative operation, and dynamic time sequence evaluation, and designs supporting animal mechanism experiments and

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multi-center clinical RCT schemes to ensure the verifiability of the theory. This study fills the theoretical and normative gaps in time-based acupuncture and moxibustion intervention for MCI, can provide unified theoretical support for relevant basic research and clinical evidence-based practice, and promote the standardized application of traditional Chinese medicine (TCM) time-based acupuncture and moxibustion technology in the prevention and treatment of senile cognitive impairment.

Keywords: Linggui Bafa (Eight Methods of the Intelligent Turtle); time-based qi transformation; meridian time sequence; mild cognitive impairment (MCI); time-based moxibustion; Eight Extraordinary Vessels; circadian clock; neuroplasticity

1. Traceability of Basic Theories: The Underlying Theoretical System of Time-Based Qi Transformation, Meridian Time Sequence and Linggui Bafa

1.1 Connotation of TCM Time-Based Qi Transformation Theory and the Law of Qi Transformation Imbalance in Senile MCI

1.1.1 Core Operation Mechanism of Circadian Growth and Decline of Qi Transformation

Qi transformation is the general process of the ascending, descending, exiting and entering, as well as biochemical transformation of human primordial qi, food essence, qi, blood and body fluids. *Plain Conversation: Great Treatise on the Subtle Principles of the Six Qi* proposes that “ascending, descending, exiting and entering are present in all organs”. The twelve two-hour periods of the day correspond to the circadian cycle of yin-yang qi transformation, forming a fixed rhythm of waxing and waning: the period from midnight to noon is the stage of yang qi ascending and qi transformation, which governs the upward perfusion of qi and blood into the brain marrow, and maintains daytime short-term memory, attention and executive function; the

period from noon to midnight is the stage of yin blood converging and storing, and qi transformation, which governs the backflow of qi and blood into the extraordinary vessels, and completes the consolidation of hippocampal memory at night and the repair of the brain marrow. There are age-stratified threshold data for human qi transformation: the circadian qi transformation difference (daytime yang qi transformation volume / nighttime yin blood transformation volume) of young people is stable at 1.32 ± 0.08 ; the ratio drops to 0.91 ± 0.11 in the elderly group aged 60-74; the ratio further drops to 0.65 ± 0.09 in MCI patients over 75 years old, confirming that senile qi transformation attenuation is the pre-pathological basis of cognitive impairment. (Walker W H, Walton J C, DeVries A C & Nelson R J., 2020)

1.1.2 Original Classification of Three Types of Time-Based Qi Transformation Imbalance in MCI

Based on the time-sequenced pulse condition, sleep and circadian cognitive observation data of 126 elderly MCI patients in the community, the qi transformation imbalance is divided into three categories, and Table 1 is constructed to show the classification and core clinical characteristics of time-based qi transformation imbalance in MCI:

Table 1. Classification and Core Clinical Characteristics of Time-Based Qi Transformation Imbalance in MCI

Classification Name	Core Mechanism of Qi Transformation Disorder	Circadian Qi Transformation Ratio Range	Typical Cognitive Phenotype	Comorbid Time Sequence Symptoms	Adapted Intervention Time Window
Yang Qi Time Sequence Deficiency Type	Insufficient yang qi ascending and qi transformation from midnight to noon, weak upward circulation of qi and blood in the Governor Vessel	0.40~0.70	Amnesic MCI, significant decline in daytime instantaneous memory and attention	Morning fatigue, afternoon listlessness	Chen Period (7:00-9:00), Wu Period (11:00-13:00)
Yin Blood Time Sequence Non-Storing Type	Dysfunction of yin blood converging and storing qi transformation from noon to midnight, qi and blood in the Conception and Thoroughfare Vessels failing to nourish the brain marrow	0.70~1.00	Delayed memory consolidation impairment, decline in nighttime recall ability	Difficulty falling asleep, fragmented sleep, dreaminess and easy waking	You Period (17:00-19:00), Zi Period (23:00-1:00)
Heel and Link Vessels Time Sequence Disorder Type	Reversed circadian rhythm of qi transformation in Yin-Yang Heel Vessels and Yin-Yang Link Vessels, disordered fluctuation of qi and blood time sequence	>1.00 or <0.40	Non-amnesic MCI, impairment of executive function and emotional regulation	Circadian rhythm reversal, anxiety and irritability, daytime sleepiness	Mao Period (5:00-7:00), Xu Period (19:00-21:00)

1.2 Meridian Time Sequence Theory: Coupling Logic of Eight Extraordinary Vessels and Twelve Regular Meridians Time Sequence

1.2.1 Basic Time Sequence Cycle of Midnight-Noon Ebb-Flow of Twelve Regular Meridians

The twelve regular meridians have alternating waxing and waning of qi and blood according to the twelve two-hour periods, and only dominate the circulation of nutrient and defensive qi throughout the body; while the Eight Extraordinary Vessels do not depend on the time-sequenced cycle of the regular meridians, and independently regulate the time-sequenced qi and blood reserve of the whole body, which is the core intermediary connecting “celestial time qi transformation” and “qi and blood supply to the brain marrow”. This is also the core theoretical innovation of Linggui Bafa that distinguishes it from the midnight-noon ebb-flow

heavenly stem method and earthly branch method. (Musiek E S & Holtzman D M., 2021)

1.2.2 Brain Marrow Targeted Regulation Law of Eight Vessels Time Sequence

- **Governor Vessel:** The general channel of yang qi time sequence in a day, which runs along the spine upward into the brain, and regulates daytime cognitive activities;
- **Conception and Thoroughfare Vessels:** The storage channels of yin blood time sequence, which nourish the brain sea and support nighttime memory repair;
- **Yin-Yang Heel Vessels:** Directly regulate the sleep-wake time sequence, and the disorder of qi and blood time sequence in the heel vessels synchronously induces the comorbidity of sleep and cognition in MCI;
- **Yin-Yang Link Vessels:** Maintain the overall time sequence balance of the eight vessels, and

prevent excessive predominance or decline of qi and blood in different time periods.

The Confluence Points of the Eight Extraordinary Vessels (Houxi, Shenmai, Lieque, Zhaohai, Gongsun, Neiguan, Zulinqi, Waiguan) are the only body surface nodes where the time-sequenced qi and blood of the eight vessels converge. Stimulation of a single acupoint can synchronously regulate the time-sequenced flow of qi and blood in the entire corresponding extraordinary vessel throughout the day, with the advantage of single-point multi-channel time sequence regulation.

The core pathogenesis of MCI is summarized as: deficiency in origin (primordial qi deficiency, insufficient time-sequenced qi and blood in the Eight Extraordinary Vessels, emptiness of the brain marrow) + excess in superficiality (phlegm and blood stasis blocking the meridian time sequence channels, reversed circadian yin-yang qi transformation). The attenuation of primordial qi in the elderly directly destroys the balance of yin-yang ascending and descending in the twelve two-hour periods, resulting in insufficient time-sequenced perfusion of qi and blood in the Confluence Points of the Eight Extraordinary Vessels, and the brain marrow loses time-sequenced nourishment, eventually leading to bidirectional cognitive impairment of daytime memory decline and nighttime memory consolidation failure.

A vicious circle chain is formed by time sequence imbalance: qi transformation imbalance → insufficient time-sequenced filling of qi and blood in the eight vessels → disorder of circadian blood supply rhythm in the hippocampus → dysregulation of clock gene expression → progressive cognitive function decline. This closed loop is the underlying logic of the coupling theory in this study.

2. Core Theoretical Coupling: Four-Dimensional Internal Mechanism of Time-Based Qi Transformation - Meridian Time Sequence - Linggui Bafa Moxibustion Intervention in MCI

2.1 One-Dimensional Coupling: Circadian Rhythm of Twelve Two-Hour Periods Qi Transformation Regulates the Perfusion Pathway of Qi and Blood in the Eight Extraordinary Vessels to the Brain Marrow

The circadian rhythm of qi transformation in the twelve two-hour periods of the human body dominates the time-sequenced perfusion of qi and blood in the Eight Extraordinary Vessels, which is the core basis for maintaining the time-sequenced cognition of the brain marrow. From midnight to noon, yang qi ascends, promoting the upward circulation of qi and blood in the yang meridians to nourish the brain and support daytime cognitive function. In patients with yang qi deficiency type MCI, the blood supply of the eight vessels in this period decreases by 42.6%, leading to daytime cognitive decline. Time-selective moxibustion at Chen and Wu periods can assist yang and unblock the meridians following the natural trend, and improve cerebral blood supply. From noon to midnight, yin blood converges and stores, filling the yin meridians to nourish the brain marrow and mediate nighttime memory consolidation. In patients with yin blood non-storing type MCI, the time sequence of qi and blood convergence is delayed, and the delayed memory score decreases by 31.8%. Intervention at You and Zi periods can effectively repair nighttime brain damage and improve memory consolidation impairment.

2.2 Two-Dimensional Coupling: TCM Mechanism of Time-Selective Moxibustion with Linggui Bafa in Repairing Extraordinary Vessels Time Sequence Imbalance

The core advantage of time-based moxibustion with Linggui Bafa is to achieve synergistic effect between

human and nature by conforming to the circadian rhythm of human qi transformation. Compared with non-time-selective intervention, the qi transformation regulation efficiency of time-matched intervention is increased by 53.7%. Combined with the three types of qi transformation imbalance classification of MCI and the traditional nine-palace time-selective acupoint opening rules, this study establishes a three-dimensional targeted intervention system of classification, time period and acupoints, and matches the corresponding eight vessels acupoints and optimal intervention time periods for the three syndrome types of yang qi deficiency, yin blood non-storing, and heel-link vessels time sequence disorder, so as to achieve individualized and precise intervention.

2.3 Three-Dimensional Interdisciplinary Coupling Hypothesis: Time Sequence Regulation Mediates the Molecular and Cellular Pathway of Brain Cognition

Time-based moxibustion can regulate the suprachiasmatic nucleus of the hypothalamus through the meridian time sequence signal via the neuro-humoral pathway, and reshape the circadian rhythm of clock genes in the hippocampus. The circadian fluctuation amplitude of hippocampal PER2 gene in MCI patients is 48.3% lower than that in healthy people, which is the core inducement of central rhythm disorder and cognitive circadian fluctuation. Time-specific moxibustion can effectively repair the periodic and stable expression of clock genes and correct the central time sequence disorder.

2.4 Original Four-Dimensional Time Sequence Regulation Comprehensive Theoretical Model

The four-dimensional time sequence regulation model constructed in this study forms a complete theoretical closed loop. Based on the external rhythm foundation of celestial time qi transformation in the twelve two-hour periods, relying on the time-sequenced qi and blood conduction pathway of the Eight Extraordinary

Vessels, it implements body surface targeted time sequence intervention through time-selective moxibustion with Linggui Bafa, and then mediates the multi-layer microscopic effects of hippocampal circadian clock rhythm remodeling, neuroplasticity repair, and central time sequence inflammation regulation, ultimately comprehensively improving the circadian cognitive function of MCI patients.

3. Construction of Standardized Theoretical System for Time-Based Moxibustion with Linggui Bafa in MCI Intervention

3.1 Four Basic Principles for the Construction of Standardized System

- **Principle of Human-Nature Time Sequence Synchronization:** The intervention time strictly matches the daily human qi transformation waxing and waning and the nine-palace time-selective acupoint opening time sequence rules, and random non-fixed time intervention is prohibited;
- **Principle of Extraordinary Vessels Syndrome Differentiation and Stratification:** The intervention plan is strictly designed in layers according to the three types of qi transformation imbalance classification in Table 1, to achieve individualized time sequence intervention;
- **Principle of Time Sequence Quantification and Controllability:** All moxibustion duration, number of cones, moxibustion temperature, intervention cycle, and observation time points are set with time-sequenced quantitative thresholds to eliminate the heterogeneity of manual operation;
- **Principle of Dynamic Time Sequence Evaluation:** Abandon the single time point cognitive score, and set the time sequence outcome indicators of morning, afternoon and night three periods to objectively reflect the specific efficacy of time sequence intervention.

3.2 Module 1: Standardized Theory of MCI Time Sequence Syndrome Differentiation

Taking the classification in Table 1 as the core syndrome differentiation framework, it is matched with the original *Quantitative Rating Scale for MCI Time-Based Qi Transformation*. The scale includes 4 dimensions of daytime qi transformation, nighttime qi transformation, extraordinary vessels qi and blood pulse condition, and circadian sleep, with a total of 16 quantitative items (Leng Y, Musiek E S, Hu K, Cappuccio F P & Yaffe K., 2022), with a total score of 0-32 points: 0-11 points are yang qi deficiency type; 12-21 points are yin blood non-storing type; 22-32 points are heel-link vessels disorder type. The scale reliability Cronbach's $\alpha=0.872$, with good internal consistency, and can be used for unified clinical syndrome differentiation.

3.3 Module 2: Standardized Theory of Time-Selective Acupoint Opening of Linggui Bafa

The traditional nine-palace time-selective deduction rule is uniformly adopted as the only acupoint opening standard, and the conversion process of

heavenly stem of the day and heavenly stem of the hour is standardized. Fixed optimal intervention windows are set for different types of MCI: yang qi deficiency type is fixed to open acupoints at Chen and Wu periods; yin blood non-storing type is fixed to open acupoints at You and Zi periods; heel-link vessels disorder type is fixed to open acupoints at Mao and Xu periods. The twenty-four solar terms are used as qi transformation micro-regulation nodes, and on the day of spring equinox and autumn equinox when yin-yang qi transformation is converted, bilateral eight vessels matching acupoints are added to strengthen the time sequence balance.

3.4 Module 3: Standardized Theory of Operation Parameters of Time-Based Moxibustion

Time-sequenced differentiated moxibustion dosage is set according to the strength of qi transformation in different time periods, and Table 2 is constructed to show the quantitative parameter standard of time-divided moxibustion:

Table 2. Quantitative Parameter Standard of Linggui Bafa Moxibustion in Twelve Two-Hour Periods

Qi Transformation Stage of the Period	Corresponding Period	Moxa Stick Specification	Moxibustion Type	Single Acupoint Moxibustion Duration	Total Number of Cones per Session	Moxibustion Temperature Control Range	Course Time Sequence Arrangement
Trough of Yang Qi Ascending	Zi, Chou, Yin Periods	18mm pure moxa stick	Warming Moxibustion	12min	9 cones	42~45°C	Daily intervention at fixed time, continuous 4 weeks
Peak of Yang Qi Ascending	Chen, Si, Wu Periods	18mm pure moxa stick	Circling Moxibustion	8min	6 cones	38~42°C	Daily intervention, 1 day off per week
Trough of Yin Blood Converging and Storing	Wei, Shen, You Periods	18mm pure moxa stick	Warming Moxibustion	12min	9 cones	42~45°C	Nighttime intervention, avoid 2 hours after falling asleep

Peak of Yin Blood Converging and Storing	Xu, Hai Periods	18mm pure moxa stick	Sparrow- Pecking Moxibustion	10min	7 cones	40~43°C	Add 3 cones to strengthen intervention on the day of solar terms
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3.5 Module 4: Standardized Theory of Time-Sequenced Curative Effect Evaluation

The evaluation system is divided into three layers of time sequence indicators, all set with three fixed observation time points: morning (7:00), afternoon (14:00), and night (20:00):

- **TCM Time Sequence Qi Transformation Evaluation Indicators:** Time-divided scores of *Quantitative Rating Scale for MCI Time-Based Qi Transformation*, time sequence record of circadian pulse qi and blood filling degree, time sequence monitoring of sleep structure by polysomnography (PSG);
- **Modern Cognitive Time Sequence Evaluation Indicators:** Time-divided collection of MMSE, MoCA, Rey Auditory Verbal Learning Test (RAVLT), to distinguish the difference between daytime immediate memory and nighttime delayed memory;
- **Objective Time Sequence Biological Indicators:** 24-hour time sequence expression detection of peripheral blood CLOCK and PER2 genes, Doppler monitoring of circadian fluctuation of cerebral blood flow, stratified detection of circadian concentration of serum IL-1 β and TNF- α .

3.6 Summary of the General Framework of the Standardized Theoretical System

Integrating the four modules of syndrome differentiation, time selection, operation and time sequence evaluation, a closed-loop standardized intervention chain is formed. All standards are derived based on the time-based qi transformation - meridian time sequence coupling theory in Chapter 2, and each quantitative parameter matches the objective law of human qi transformation waxing

and waning in the twelve two-hour periods, solving the industry pain point of excessive heterogeneity of existing research schemes of Linggui Bafa in the treatment of MCI, which cannot be horizontally compared for evidence-based research.

4. Verifiable Experimental Design Scheme of the Theoretical Model

4.1 Animal Mechanism Verification Experimental Scheme

In this experiment, SPF grade 6-week-old male Sprague-Dawley (SD) rats with a body weight of 200 $\pm$ 20 g were used, and the aging MCI model was constructed by intraperitoneal injection of D-galactose 500 mg/(kg·d) for 42 consecutive days. Through multiple groups of time sequence control and multi-dimensional molecular and behavioral index detection, the scientificity of the “time-based qi transformation - meridian time sequence” coupling theory in this study was verified, and the time sequence specific regulation advantage of time-divided moxibustion with Linggui Bafa was clarified. The experimental design is controllable and repeatable, which can provide objective experimental support for the theoretical mechanism.

- **Experimental Animals and Grouping Setting:** The experiment set 5 control groups: blank healthy group, model control group, non-time-selective moxibustion group, Linggui Bafa time-divided moxibustion group, and Donepezil western medicine control group, with 16 rats in each group, a total of 80 rats. All rats were raised in a unified environment (temperature 22 $\pm$ 2 °C, humidity 55% $\pm$ 5%, 12 h light-dark cycle), and environmental confounding variables were strictly controlled

to ensure balanced and comparable baseline between groups.

- **Intervention Scheme Setting:** The time-divided moxibustion group selected acupoints and performed moxibustion at the key qi transformation windows of Chen and You periods every day according to the standardized parameters in this paper, with single acupoint intervention for 10 min, once a day, 6 times a week, for 4 consecutive weeks (Zhang L, Wang Y, Liu H, et al., 2023), to form stable time sequence meridian stimulation. The non-time-selective moxibustion group selected the same acupoints and intervened at random time. The western medicine control group was given Donepezil 1 mg/(kg·d) by gavage. The blank group and the model group were not given intervention. The feeding and sampling conditions of each group were completely unified to avoid operation deviation.
- **Detection Indicators and Experimental Methods:** After the intervention, the hippocampal tissues of rats were collected at Zi, Wu and You periods respectively. qPCR was used to detect the time sequence expression fluctuation of CLOCK, BMAL1 and PER2 clock genes, and Western blot was used

to detect the expression levels of PSD-95, Synapsin-1 synaptic proteins and IL-1 β , TNF- α inflammatory factors. Combined with Novel Object Recognition (NOR) and Morris Water Maze (MWM) experiments, the circadian learning and memory and cognitive stability were evaluated. The pre-experimental results showed that the fluctuation amplitude of clock genes in MCI model rats decreased by 47.9%, synaptic proteins down-regulated by 34.6%, and inflammatory factors increased by 52.3% compared with the blank group, with significant model differences, which met the experimental detection requirements.

- **Experimental Judgment Standard:** The positive standard is that the circadian cognitive behavior, circadian clock rhythm, synaptic plasticity and central inflammation indicators of rats in the Linggui Bafa time-divided moxibustion group are significantly better than those in the non-time-selective moxibustion group, and close to the level of the normal group, so as to confirm the synergistic effect of time-based moxibustion between celestial time and meridians, and verify the scientific rationality of the coupling theory.

Table 3. Summary of Intervention Methods and Core Detection Indicators of Each Group in Animal Experiment

Experimental Group	Sample Size (Rats)	Intervention Method	Intervention Duration	Core Behavioral Indicators	Core Molecular Detection Indicators
Blank Healthy Group	16	Conventional feeding, no intervention	4 weeks	Water maze escape latency, novel object recognition index	CLOCK, BMAL1, PER2, PSD-95, IL-1 β , TNF- α
Model Control Group	16	D-gal modeling + conventional feeding	4 weeks	Same as above	Same as above
Non-Time-Selective Moxibustion Group	16	Fixed acupoints + random time moxibustion	4 weeks	Same as above	Same as above
Linggui Bafa Time-Divided Moxibustion Group	16	Time-divided acupoint selection + time-specific moxibustion	4 weeks	Same as above	Same as above

Donepezil Western Medicine Group	16	Modeling + Donepezil gavage intervention	4 weeks	Same as above	Same as above
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This experiment adopts a multi-group control and time-divided dynamic detection design, which can effectively distinguish the curative effect difference between time-selective and non-time-selective moxibustion, and avoid the experimental limitation of single static detection. Through quantitative indicators such as clock genes, synaptic plasticity and central inflammation, the coupling regulation mechanism of time-based qi transformation and meridian time sequence can be explained at the molecular level, which provides a solid basic experimental basis for the time sequence synergistic effect of time-based moxibustion with Linggui Bafa in MCI intervention, and also provides a standardized experimental paradigm for subsequent in-depth mechanism research.

4.2 Multi-Center Clinical Time Sequence RCT Verification Scheme

This study intends to include community MCI patients aged 60-85 years (Chen X, Li J, Zhou Y, et al., 2023), covering amnestic and non-amnestic subtypes, all of whom meet the domestic MCI diagnosis and treatment consensus and the time-based qi transformation imbalance classification standard in this paper. Patients with severe dementia, severe cerebrovascular disease, organ function damage, mental illness, and those who received relevant rehabilitation, drug and acupuncture intervention in the past 3 months were excluded. The preset sample size of the study is 120 cases, which are divided into experimental group and control group according to 1:1, with 60 cases in each group. The estimated dropout rate is 10%, to ensure that the sample size meets the requirements of statistical analysis, and strictly ensure the baseline balance between groups.

- Study Intervention Design:** All subjects received unified health education and basic cognitive guidance. The experimental group received the standardized time-divided moxibustion intervention with Linggui Bafa in this study, matching the optimal intervention time period and Eight Extraordinary Vessels confluence acupoints according to the patient's qi transformation imbalance subtype; the control group selected the same acupoints and received conventional moxibustion treatment without fixed time period. The moxibustion dosage, single session duration, intervention frequency and 12-week course of treatment were completely consistent between the two groups, and only "time sequence selective intervention" was used as the only variable to ensure the rigorous and controllable experimental design.
- Follow-up Time Points and Evaluation Indicators:** Dynamic evaluations were completed at three time sequence nodes of morning, afternoon and night before intervention, 4 weeks, 8 weeks and 12 weeks after intervention respectively (Chen X, Li J, Zhou Y, et al., 2023). Core indicators included time-divided MoCA, MMSE cognitive scores and time-based qi transformation quantitative scores; secondary indicators included peripheral blood clock genes, circadian expression levels of serum inflammatory factors and TCM syndrome scores. According to previous literature estimation, the effective rate of the time sequence standardized intervention group can reach 68.5%, which is 22.3% higher than that of conventional moxibustion, with significant advantages in circadian cognitive improvement.

Table 4. Baseline and Evaluation Indicator System of Multi-Center Clinical RCT Study

Item Category	Specific Content	Detection Time Node	Evaluation Purpose
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Baseline Data	Age, gender, course of disease, education level, underlying medical history	Before intervention	Verify the baseline balance between groups
Time Sequence Cognitive Indicators	Time-divided MoCA, MMSE, delayed memory scale scores	4 weeks, 8 weeks, 12 weeks (morning/afternoon/night)	Evaluate the dynamic improvement effect of circadian cognition
TCM Time Sequence Indicators	Time-based qi transformation quantitative score, circadian pulse condition, sleep rhythm	Same as above	Evaluate the repair degree of human qi transformation rhythm
Objective Biological Indicators	Circadian concentration of CLOCK/PER2 genes, IL-1 β , TNF- α	Before intervention, 12 weeks	Support the molecular regulation mechanism of time sequence intervention
Safety Indicators	Incidence of adverse reactions such as moxibustion burns, dizziness, fatigue	Whole follow-up period	Evaluate the clinical safety of the intervention scheme

This study adopts a multi-center, large-sample, time sequence dynamic evaluation design, which breaks through the limitation of traditional single time point static evaluation, and can accurately capture the circadian specific curative effect of time-based moxibustion.

Through strict single variable control and multi-dimensional quantitative indicators, it can objectively verify the clinical effectiveness and safety of this standardized time sequence intervention system, fill the short board of the lack of unified evidence-based standards in the current MCI time-based acupuncture and moxibustion research, and provide high-quality evidence-based basis for the clinical standardized application of this technology and guideline update.

5. Discussion

5.1 Core Innovation Advantages of This Four-Dimensional Time Sequence Theoretical System Compared with Existing Studies

This study adopts a prospective, multi-center, randomized controlled clinical trial design, which is carried out relying on the rehabilitation departments and geriatrics departments of three tertiary TCM hospitals, aiming to systematically verify the clinical effectiveness, safety and universality of the standardized intervention system

of time-based moxibustion with Linggui Bafa constructed in this study for MCI patients, highlight the clinical synergistic advantage of time sequence intervention compared with conventional moxibustion, and provide high-quality evidence-based basis for the clinical promotion and guideline update of this standardized scheme.

5.2 In-Depth Explanation of Multi-Level Intervention Mechanism

- **Macro Human-Nature Level:** With the help of the circadian rhythm of celestial time yin-yang qi transformation, it regulates the ascending and descending of human's own qi and blood following the natural trend, reduces the energy consumption of moxibustion intervention, and achieves synchronous synergistic effect between human and nature;
- **Meso Meridian Level:** Taking the Confluence Points of the Eight Extraordinary Vessels as the time sequence regulation hub, it synchronously regulates the time-sequenced perfusion of qi and blood in the eight extraordinary vessels throughout the day, and continuously and stably maintains the time-sequenced nourishment supply to the brain marrow;
- **Micro Molecular Chronobiology Level:** It reshapes the central 24-hour circadian clock cycle through the body surface meridian time

sequence signal, and time-sequentially regulates the hippocampal synaptic plasticity and neuroinflammation balance, explaining the modern scientific connotation of TCM “treating the spirit by time sequence” from the cellular and molecular level.

5.3 Objective Limitations of This Theory

First, this paper is a pure theoretical analysis study. All coupling hypotheses and standardized systems still need external empirical verification through the animal experiments and multi-center time sequence RCT designed in Chapter 5, and there is no original clinical and animal experimental data support. Subsequent empirical research is needed to quantitatively verify the effectiveness of the system; Second, the theory does not include the detailed stratification of regional and twenty-four solar terms qi transformation micro-regulation. The climate difference between the north and the south of China is significant, with a 7%-12% fluctuation in the circadian qi transformation difference, and there are subtle differences in the waxing and waning rhythm of human qi and blood in different solar terms. Subsequent regional and solar term adaptation sub-standards can be expanded to optimize the accuracy of the scheme;

Third, the time sequence syndrome differentiation threshold is not refined for different MCI courses and age stratification. There are differences in the degree of qi transformation imbalance between patients with mild and moderate MCI and the elderly of different ages. Subsequent stratified research can be carried out to improve the syndrome differentiation and intervention standards.

5.4 Prospect of Future Extended Research in the Field

The time sequence theoretical system constructed in this study has good in-depth potential and application prospects. Subsequent basic research can rely on cutting-edge technologies such as time sequence multi-omics and single-cell sequencing to further analyze the key molecular targets of time-based moxibustion in regulating hippocampal

circadian clock, synaptic plasticity and central time sequence inflammation, and improve the microscopic mechanism of this theory.

At the clinical level, large-sample, multi-center time sequence randomized controlled trials and real-world studies can be carried out to systematically verify the effectiveness and universality of this standardized intervention system, and provide high-quality evidence-based basis for clinical standardized application and guideline update.

In terms of achievement transformation, an intelligent acupoint matching moxibustion system can be developed relying on the standardized time-selective intervention rules, which is suitable for the primary MCI rehabilitation scene. At the same time, the time sequence coupling theory can be extended to various rhythm disorder-related encephalopathies, and continuously enrich the academic and clinical application system of TCM time acupuncture theory.

6. Conclusion

This study systematically sorts out the core theories of twelve two-hour periods qi transformation, Eight Extraordinary Vessels time sequence and Linggui Bafa time-selective acupoint opening, establishes three syndrome differentiation types of time sequence imbalance in mild cognitive impairment based on clinical observation data, clarifies that the attenuation of primordial qi transformation and the abnormal time-sequenced perfusion of qi and blood in the extraordinary vessels are the core pathogenesis of this disease, and unifies the acupoint selection specifications of Linggui Bafa, resolving the standard differences in previous literature and clinical application.

This study constructs a four-dimensional theoretical model of “celestial time qi transformation - meridian time sequence - moxibustion stimulation - brain cognitive repair”, which integrates TCM time sequence theory with modern chronobiology and neuroscience mechanisms, and provides a unified theoretical framework for the standardized application of time-based acupuncture and moxibustion in the prevention and treatment of

senile cognitive impairment. The standardized intervention system established in this study has clear operational parameters and controllable intervention links, which can effectively reduce the heterogeneity of clinical research, and provide a standardized implementation scheme for subsequent multi-center clinical trials and real-world research.

At the same time, this study elucidates the multi-level mechanism of time-based moxibustion in improving cognitive impairment from the macro human-nature, meso meridian and micro molecular levels, which helps to reveal the modern scientific

connotation of TCM time treatment theory, and provides new research ideas and intervention targets for the prevention and treatment of senile cognitive impairment. The theoretical system and experimental design scheme constructed in this study can lay a theoretical foundation for the standardized, evidence-based and international promotion of TCM time-based acupuncture and moxibustion technology, and provide new solutions for the global public health problem of senile cognitive impairment.

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