Summary of the research program

Project Title	**Study on Brain Network Characteristics of Pain Patients Based on Magnetoencephalography (MEG)**
Study Objectives	To investigate the magnetoencephalography (MEG) characteristics of neural oscillations and functional connectivity in patients with muscle pain, to analyze the relationships between these indicators and clinical phenotypes including pain intensity, emotional status/sleep quality, disease duration, and sex, to establish a predictive model for pain outcomes, and to evaluate its predictive value for persistent pain, symptom improvement, and functional outcomes during the follow-up period, so as to identify candidate objective neural biomarkers.
Research Hypotheses	1.Patients with muscle pain exhibit distinctive neural oscillation characteristics in brain networks, which are significantly correlated with clinical phenotypes such as pain intensity, disease duration, and the severity of emotional disturbances including anxiety and depression. 2.Baseline MEG abnormalities can predict persistent pain status, the degree of pain improvement, and functional outcomes during the follow-up period.
Study Design	☑ Cohort Study □ Case-Control Study □ Cross-Sectional Study □ Case Report/Case Series
Study Participants	**Inclusion Criteria for Muscle Pain Patients:** Meets the diagnostic criteria for muscle pain as specified in the *Clinical Diagnostic Guidelines: Physical Medicine and Rehabilitation Volume*; VAS score ≥ 3; Age between 18 and 70 years; Lesions located in the soft tissues of the neck, shoulder, or lumbodorsal region, with associated tender points; Able to understand and cooperate with completion of questionnaires, MEG, and MRI examinations;

	Has signed the informed consent form. **Exclusion Criteria for Muscle Pain Patients:** History of prior cervical, shoulder, or lumbar related disorders; Recent use of medications that significantly affect central nervous system excitability with unstable disease control; Contraindications to MEG or MRI; Presence of ferromagnetic metal implants in the body (e.g., metal dentures, aneurysm clips, pacemakers, stents, plates, etc.), claustrophobia that precludes MEG examination, or failed MEG acquisition; Concurrent severe cardiac, cerebral, renal, or other systemic diseases; History of muscle diseases such as tuberculosis, rheumatism, or infection; Significant cognitive deficits or communication impairments that prevent cooperation with this study. **Inclusion Criteria for Healthy Controls:** Age between 18 and 70 years; Has signed the informed consent form. **Exclusion Criteria for Healthy Controls:** Presence of electrically conductive, ferromagnetic, or other magnetically sensitive metal implants in the head or neck.
Diagnostic Criteria	Meets the diagnostic criteria for muscle pain as specified in the Clinical Diagnostic Guidelines: Physical Medicine and Rehabilitation Volume.
Sample Size and Calculation Basis	This study primarily enrolls participants with pain, employing a prospective cohort design with healthy controls serving as a baseline reference group. The sample size for pain participants is estimated based on the requirements of longitudinal follow-up analyses and predictive model development. Given that this study plans to incorporate multiple dimensional candidate predictors, including demographic characteristics, clinical scale measures, and MEG-derived neural oscillation and functional connectivity metrics, a principle of "at least 15–20 outcome events per candidate predictor" was adopted for the initial estimation to

	mitigate the risk of model overfitting and ensure model stability. Let p denote the number of candidate predictors, ϕ denote the primary outcome event rate, and L denote the loss to follow-up rate. The planned sample size for pain participants is estimated using the following formula: $N=k\times p/\phi\times(1-L)$.where k = 15–20 and L = 20%. Taking into account the practical needs of this study, including baseline comparisons, stratified analyses by different pain types, 6-month longitudinal follow-up, and predictive model development, we plan to enroll no fewer than 1,000 pain participants, with the expectation of obtaining at least 800 valid cases that complete the 6-month follow-up. Healthy controls are not part of the primary follow-up cohort. Their sample size is determined separately based on the need to establish a baseline brain network reference range and perform between-group comparisons at baseline. We plan to enroll approximately 200 healthy controls to construct reference characteristics of brain networks in the healthy population and provide a normative reference for assessing the degree of abnormality in pain participants.
Primary Exposure Factors	Demographic and socioeconomic factors: age, sex, BMI, educational level, etc. Lifestyle factors: physical activity, sleep status, etc. Psychosocial factors: depression/anxiety, stress, etc. Occupational and ergonomic factors: prolonged sitting/prolonged standing, heavy lifting/carrying, postural load, etc. Health status and medical history: chronic disease comorbidities, trauma/surgery history, medication history, etc.
Outcome Variables	**Primary Outcome Variable:** Visual Analogue Scale (VAS) score **Secondary Outcome Variables:** McGill Pain Questionnaire (MPQ) Hamilton Anxiety Scale (HAMA)

	Hamilton Depression Scale (HAMD) Pittsburgh Sleep Quality Index (PSQI) Oswestry Disability Index (ODI) Neck Disability Index (NDI) Shoulder Pain and Disability Index (SPADI) American Orthopaedic Foot & Ankle Society Ankle-Hindfoot Scale (AOFAS-AH) International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Disabilities of the Arm, Shoulder and Hand Scale (DASH) MEG source localization and fMRI blood oxygen level-dependent (BOLD) signal intensity and activation strength, etc.
Follow-up Plan	This study employs a prospective cohort design with regular follow-up of all enrolled participants. Follow-up assessments encompass general health status, changes in exposure factors, primary and secondary outcome measures, and adverse events. Follow-up will be carried out by telephone or electronic methods. Rigorous follow-up management strategies will be applied to reduce attrition, and any cases of loss to follow-up will be recorded and subjected to statistical analysis to guarantee the validity and reliability of the study findings.
Sample Collection	☑ No □ Yes
Non-Medical Purpose Examinations	☑ No □ Yes (e.g., unnecessary CT scans, contrast imaging, laboratory tests, etc.)
Statistical Methods	Descriptive statistics will be used to summarize baseline characteristics. For between-group comparisons, continuous variables will be analyzed using t-tests or rank-sum tests, and categorical variables using chi-square or Fisher's exact tests, with multivariate models applied to adjust for

	confounders such as age and sex when necessary. Pain outcomes will be determined based on VAS scores (VAS ≥ 3 coded as 1, < 3 coded as 0). Predictive models will be developed using clinical data and MEG features, with data stratified by a 1:1 ratio into training and test sets using stratified random sampling. Penalized regression or dimensionality reduction techniques will be applied to high-dimensional features to mitigate overfitting. Model performance will be evaluated using the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals, sensitivity, and specificity. Calibration curves will be plotted (with calibration intercept/slope, and Brier score optional). Bootstrap resampling will be used for internal validation and optimism correction. If an independent cohort is available, external validation will be performed, with recalibration or model updating as needed. For MEG comparisons across multiple brain regions and frequency bands, the false discovery rate (FDR) or permutation methods will be used to control for multiple comparisons. Missing data will be described and, if necessary, handled using multiple imputation. A two-sided significance level of $\alpha = 0.05$ will be applied.
Self-Assessment of Research Risk Level	□ High Risk □ Moderate Risk ☑ Low Risk **Brief Justification:** The interventions in this study pose minimal safety risks. Magnetoencephalography (MEG) involves a weak magnetic field environment and is a non-invasive, radiation-free procedure that carries virtually no additional risk.

Confidentiality Statement:

The information contained in this research protocol is provided solely for review by the investigators of this project, the Clinical Research Management Committee, and relevant regulatory agencies. No information may be disclosed to any third party unrelated to this study without prior approval from the Principal Investigator.

1.Research Background

Pain is a subjective and complex experience that involves not only peripheral neural input but also the participation and integration of multiple functional brain networks. Pain, particularly chronic pain, significantly affects participants' quality of life and is associated with various physical and psychological issues, including sleep disturbances and emotional distress, making it a serious public health concern [1]. Traditional pain assessment relies primarily on participants' self-reports; however, this subjective approach fails to accurately reflect the true neural activity and network states underlying pain, thereby limiting the advancement of pain mechanism research and therapeutic efficacy evaluation. Consequently, researchers have proposed the use of functional brain imaging techniques to explore objective neurophysiological biomarkers of pain [2].

The perception and processing of pain involve complex neural network activities across multiple brain regions, encompassing sensory, emotional, and cognitive functional subnetworks [3]. Studies have demonstrated that brain connectivity patterns undergo reorganization during pain states, with functional connectivity and topological properties of brain networks showing significant differences in pain participants, suggesting that pain is not merely a localized sensory response but a complex process involving global network reorganization [1, 4]. Numerous neuroimaging studies using resting-state functional magnetic resonance imaging (rs-fMRI) and other techniques have revealed significant connectivity abnormalities in intrinsic brain networks—such as the default mode network, sensory, and cognitive networks—in chronic pain participants. These aberrant connections are closely associated with pain intensity and the maintenance mechanisms of chronic pain [1, 2]. Electroencephalography (EEG) and magnetoencephalography (MEG) enable direct measurement of neural electrical activity [5] and allow analysis of neural oscillatory dynamics related to pain, providing oscillatory band features associated with pain cognition, emotional regulation, and pain perception processing. Notably, oscillations in the theta, alpha [6], beta, and gamma bands are closely linked to pain intensity and alterations in brain functional states [7]. MEG, owing to its high temporal resolution in capturing magnetic brain activity, is

considered an effective tool for investigating pain-related brain network dynamics. MEG recordings reflect the synergistic activity of neural networks at different frequencies, helping to reveal the transient interaction patterns of neuronal populations during pain processing [8]. Compared with other modalities, MEG offers unique advantages in capturing brain network topology and oscillatory patterns. Combined with graph theory-based analytical approaches, it can assess functional connectivity and clustering effects in pain-related brain networks, thereby quantifying alterations in network organizational structure—such as reduced local efficiency or changes in global integration—which are particularly pronounced in chronic pain participants [1, 9].

In chronic pain, neural oscillations at different frequencies reflect distinct aspects of brain functional status. For instance, the theta band is often associated with attentional and emotional modulation of pain, whereas beta and gamma bands are more likely related to the cognitive integrative processes of pain. These oscillatory features can be more directly observed through MEG or EEG [5, 7]. Different types of pain, such as chronic back pain and fibromyalgia, exhibit differences in brain network organization and dynamic oscillatory characteristics, suggesting that the neural mechanisms of pain possess certain diagnostic specificity, providing a theoretical basis for comparative studies across pain types [10]. The impact of treatment on brain networks is a core issue in understanding pain processing mechanisms. Interventions such as transcranial magnetic stimulation and cognitive-behavioral therapy may reshape brain networks and alter pain-related connectivity patterns and excitability, with MEG being used to evaluate these network-level treatment effects [11].

Cognitive-behavioral interventions have shown that changes in brain network activity patterns occur in chronic pain participants following treatment, suggesting that therapy can reduce pain perception by modulating brain network dynamics. These changes are observable in MEG recordings as frequency-specific oscillatory adjustments [11]. Existing studies indicate that brain functional connectivity and network topological metrics in pain participants exhibit measurable changes before and after clinical interventions, and these changes are often correlated with the degree of pain relief, emotional improvement, or pain-related cognitive adjustments [12, 13]. In

pain research, the integration of multimodal imaging techniques such as MEG and fMRI can provide a comprehensive reflection of neural dynamics across different temporal and spatial scales, offering a more holistic analytical framework for identifying neural markers and elucidating the complex network processes underlying pain processing [2].

Topological features of pain networks—such as modularity, local efficiency, and global integration—are important metrics for assessing excessive integration or dysregulation in the brain during pain processing. In chronic pain participants, alterations in these topological features may be closely associated with pain memory, attentional bias, and emotional processing [14]. Although numerous neuroimaging studies have revealed pain-related changes in brain networks, there remains a lack of consistent objective biomarkers for distinguishing different pain types and evaluating the effects of various treatment modalities on brain networks. Therefore, conducting in-depth MEG-based research is of significant importance [15, 16].

The present study proposes to employ zero-field MEG technology to capture neural oscillations and functional connectivity features with greater precision under extremely low magnetic interference conditions. This approach aims to refine the characterization of brain network differences across pain types and to evaluate the modulatory effects of different treatment modalities on brain network excitability, thereby providing highly sensitive neural indicators for pain mechanism research [17, 18]. By integrating MEG recordings with analytical methods—including oscillatory spectral analysis, functional connectivity assessment, and network topology measurement—this study seeks to elucidate the stability of pain-related brain networks and their response patterns to therapeutic interventions. The findings are expected to provide experimental evidence for a deeper understanding of the neural mechanisms of pain and to establish fundamental neural network metrics for future personalized pain management [19].

2.Research Questions and Research Objectives

Research Questions:

Does pain have reproducible objective neural biomarkers as measured by magnetoencephalography (MEG)? Can these brain network features serve as objective neural biomarkers reflecting clinical phenotypes such as pain intensity, disease duration, and emotional/sleep status? Furthermore, can a pain outcome prediction model—equally valid in external datasets—be constructed based on neural oscillation and functional connectivity characteristics, thereby providing a basis for stratified pain management?

Research Objectives:

(1) Overall Objective:

To establish a prospective follow-up cohort primarily composed of pain participants using MEG technology, with a healthy control reference group, to identify baseline brain network characteristics across different pain types, to screen for objective neural biomarkers, and to evaluate their predictive value for pain persistence, symptom improvement, and functional outcomes.

(2) Specific Objectives:

1) To compare baseline MEG-derived neural oscillation and functional connectivity differences between pain participants and healthy controls, as well as among participants with different pain types, and to construct predictive models incorporating clinical information to evaluate their discriminative ability for pain persistence status and outcomes during the follow-up period.

2) To analyze the relationships between baseline MEG abnormalities and VAS scores, disease duration, functional limitations, sleep quality, and emotional scale measures, and to evaluate their predictive role in subsequent symptom changes and the magnitude of functional improvement.

3. Research Methods

3.1 Study Design

This project is a single-center prospective cohort study. Pain participants with a baseline VAS score $\geqslant$ 3 will be consecutively enrolled into the follow-up cohort, while healthy controls matched for age and sex frequency will be recruited as a baseline reference group. After completing MEG, MRI, and clinical scale assessments, pain

participants will be stratified according to pain type, disease duration, and severity, with repeated collection of pain and functional outcomes during follow-up. Healthy controls will complete baseline MEG, MRI, and clinical scale assessments and will not be included in the primary longitudinal follow-up analysis.

3.2 Study Setting and Study Participants

This study will enroll pain participants, who will be primarily recruited from outpatient clinics and inpatient wards.

Inclusion Criteria:

(1) Meets the diagnostic criteria for muscle pain as specified in the Clinical Diagnostic Guidelines: Physical Medicine and Rehabilitation Volume;

(2) Age between 18 and 70 years;

(3) VAS score $\geqslant$ 3;

(4) Lesions located in the soft tissues of the neck, shoulder, or lumbodorsal region, with associated tender points;

(5) Able to understand and cooperate with completion of questionnaires, MEG, and MRI examinations;

(6) Has signed the informed consent form.

Exclusion Criteria:

(1) History of prior cervical, shoulder, or lumbar related disorders;

(2) Recent use of medications that significantly affect central nervous system excitability with unstable disease control;

(3) History of major neurological disorders or severe psychiatric disorders;

(4) Contraindications to MEG or MRI, including the presence of ferromagnetic metal implants in the body (e.g., cardiac pacemakers, hearing aids, carotid artery stents, etc.), claustrophobia that precludes MEG examination, or failed MEG acquisition;

(5) Concurrent severe cardiac, cerebral, renal, or other systemic diseases;

(6) History of muscle diseases such as tuberculosis, rheumatism, or infection;

(7) Significant cognitive deficits or communication impairments that prevent cooperation with this study.

Inclusion Criteria for Healthy Controls:

(1) Age between 18 and 70 years;

(2) Has signed the informed consent form.

Exclusion Criteria for Healthy Controls:

(1) Presence of electrically conductive, ferromagnetic, or other magnetically sensitive metal implants in the head or neck.

3.3 Study Variables (Factors) and Measurements

(1) Demographic and socioeconomic factors: age, sex, BMI, educational level, etc.

(2) Lifestyle factors: physical activity, sleep status, etc.

(3) Psychosocial factors: depression/anxiety, stress, etc.

(4) Occupational and ergonomic factors: prolonged sitting/prolonged standing, heavy lifting/carrying, postural load, etc.

(5) Health status and medical history: chronic disease comorbidities, trauma/surgery history, medication history, etc.

3.4 Study Outcomes

Primary Outcome Variable:VAS score

Secondary Outcome Variables McGill Pain Questionnaire (MPQ), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), Pittsburgh Sleep Quality Index (PSQI), Oswestry Disability Index (ODI), Neck Disability Index (NDI), Shoulder Pain and Disability Index (SPADI), American Orthopaedic Foot & Ankle

Society Ankle-Hindfoot Scale (AOFAS-AH), International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Disabilities of the Arm, Shoulder and Hand Scale (DASH), MEG, MRI

3.5 Follow-up (for Cohort Studies)

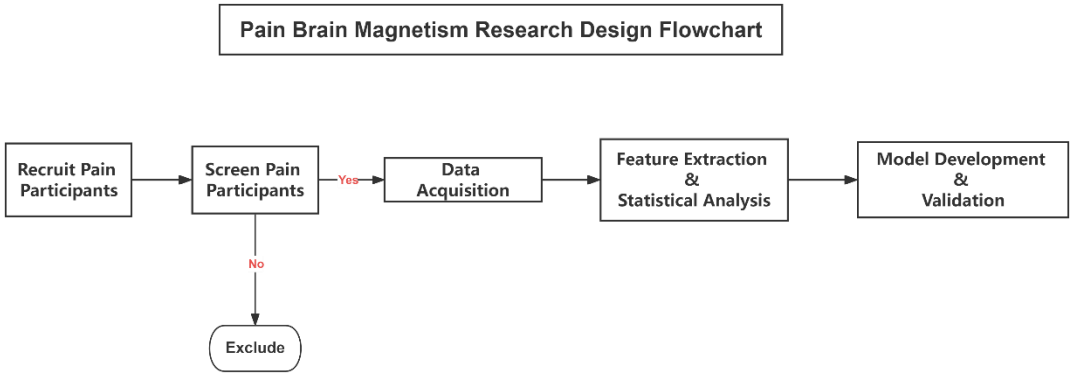
This study adopts a prospective cohort design and conducts regular follow-up of enrolled participants. The follow-up content includes general condition, changes in exposure factors, primary and secondary outcome measures, and adverse events. Follow-up will be conducted by telephone. Comprehensive follow-up management measures will be implemented to minimize loss to follow-up, and any loss to follow-up will be documented and statistically analyzed to ensure the reliability of the study results.

3.6 Sample Size

This study primarily enrolls participants with pain, employing a prospective cohort design with healthy controls serving as a baseline reference group. The sample size for pain participants is estimated based on the requirements of longitudinal follow-up analyses and predictive model development. Given that this study plans to incorporate multiple dimensional candidate predictors, including demographic characteristics, clinical scale measures, and MEG-derived neural oscillation and functional connectivity metrics, a principle of "at least 15–20 outcome events per candidate predictor" was adopted for the initial estimation to mitigate the risk of model overfitting and ensure model stability. Let p denote the number of candidate predictors, ϕ denote the primary outcome event rate, and L denote the loss to follow-up rate. The planned sample size for pain participants is estimated using the following formula: $N=k\times p/\phi\times(1-L)$.where k = 15–20 and L = 20%. Taking into account the practical needs of this study, including baseline comparisons, stratified analyses by different pain types, 6-month longitudinal follow-up, and predictive model development, we plan to enroll no fewer than 1,000 pain participants, with the expectation of obtaining at least 800 valid cases that complete the 6-month follow-up.

Healthy controls are not part of the primary follow-up cohort. Their sample size is determined separately based on the need to establish a baseline brain network reference range and perform between-group comparisons at baseline. We plan to enroll 200 healthy controls to construct reference characteristics of brain networks in the healthy population and provide a normative reference for assessing the degree of abnormality in pain participants.

3.7 Study Technical Flowchart



3.8 Data Collection and Management

MEG measurements must be completed within a magnetic shielding device. In an ultra-weak magnetic environment approaching zero magnetic field, atomic spin magnetometers are used to measure and record the weak magnetic fields naturally generated by cerebral electrical activity. The currents that generate the cerebral magnetic field are predominantly intracellular currents; although extracellular currents can flow over a wider range, their current density is relatively low and the magnetic fields they produce are weaker. Therefore, the signals recorded by MEG primarily reflect the magnetic fields generated by intracellular currents, while the contribution of extracellular currents to MEG results is negligible.

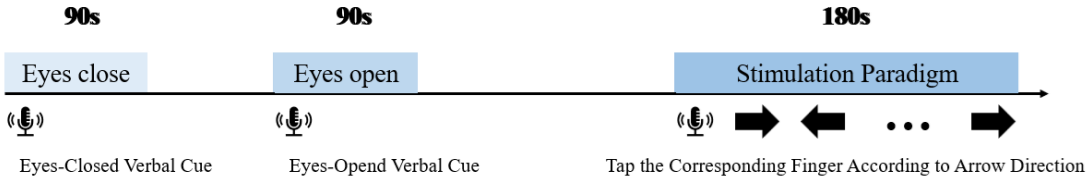
MEG scanning does not require injection of contrast agents and is a non-contact, non-invasive, and rapid detection method. It is not affected by tissue conductivity, offers high temporal resolution, and possesses good spatial localization capability. By coregistration with cranial MRI structural images, the brain regions corresponding to

the probe signals can be identified. Further power spectrum analysis of MEG signals across different frequency bands allows for the assessment of spectral distribution characteristics, thereby providing evidence for inferring abnormal brain regions and potential lesion-related sites.

After enrolling participants who meet the inclusion criteria, researchers will complete the informed consent process in a timely manner. For healthy volunteers, health questionnaire assessments will be conducted, and MEG examinations will be coordinated and scheduled. Clinical information and relevant imaging data will also be collected. All data will be systematically organized, periodically aggregated, and properly preserved by the research team, with regular verification and supplementation as needed throughout the study.

(1) MEG Data

Experimental Paradigm:The total paradigm duration is 10 minutes, divided into two phases of measurement, including 4 minutes of working memory task MEG measurement, 1.5 minutes of eyes-closed MEG measurement, 1.5 minutes of eyes-open MEG measurement, and 3 minutes of stimulation-evoked MEG measurement. All measurements are accompanied by voice and text prompts. The working memory measurement requires participants to press a button with their right hand when identical numbers appear. The evoked stimulation measurements include pure-tone auditory stimulation, picture-flashing visual stimulation, and finger movement tasks. If participants have difficulty cooperating with the finger movement tasks, these may be omitted.



(2) Cranial MRI

MRI examinations will be performed before and after MEG data acquisition for coregistration purposes in MEG analysis. At other time points, additional MRI scans

may be performed as needed based on the participant's clinical condition or study requirements to facilitate analysis coregistration.

(3) Scale/Questionnaire Assessments

A. McGill Pain Questionnaire (MPQ)

Scoring criteria:a. Pain quality score: Based on 20 adjectives, each rated 0–3, reflecting pain characteristics; scores are summed.b. Pain intensity score: Participant self-rating from 0 to 5, where 0 = no pain and 5 = extreme pain.c. Pain quality subscore ranges from 0 to 78, and pain intensity subscore ranges from 0 to 5. The total score is the sum of these two subscores.

B. Hamilton Anxiety Scale (HAMA)

Scoring criteria:a. Consists of 14 items, each rated according to symptom severity on a scale of 0 to 4, where 0 = absent, 1 = mild, and 4 = extremely severe.b. Total score is the sum of all item scores, ranging from 0 to 56. Interpretation: 0–17 = mild anxiety; 18–24 = moderate anxiety; ≥25 = severe anxiety.c. The scale primarily assesses the type and severity of anxiety symptoms, aiding clinical judgment of anxiety levels.

C. Hamilton Depression Scale (HAMD)

Scoring criteria:a. This scale is used to assess the symptoms and severity of depression. It consists of 17 items, each rated 0–4 according to symptom severity (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe).b. Total score is the sum of all 17 items, ranging from 0 to 52. Interpretation: 0–7 = no or minimal depression; 8–13 = mild depression; 14–18 = moderate depression; ≥19 = severe depression.

D. Pittsburgh Sleep Quality Index (PSQI)

Scoring criteria:a. This scale assesses sleep quality over the past month. It consists of 19 self-rated items and 5 items rated by a spouse/roommate (the latter are not included in the total score). Each self-rated item is scored 0–3, where 0 = no problem and 3 = most severe problem.b. Total score is the sum of the 19 self-rated items, ranging from 0 to 21. Higher scores indicate worse sleep quality. Interpretation: 0–5 = good

sleep quality; 6–10 = mild sleep disturbance; 11–15 = moderate sleep disturbance; ≥16 = severe sleep disturbance.

E. Oswestry Disability Index (ODI)

Scoring criteria:a. This scale assesses functional disability due to low back pain. It consists of 10 items covering various aspects of daily living activities, each rated 0–5 (0 = no impact, 1 = mild impact, 2 = moderate impact, 3 = severe impact, 4 = extreme impact, 5 = unable to perform the activity). One answer is selected for each item, and scores are summed.b. Total raw score ranges from 0 to 50. The final score is expressed as a percentage: ODI (%) = (sum of item scores / 50) × 100%. Interpretation: 0–20% = mild disability; 21–40% = moderate disability; 41–60% = severe disability; 61–80% = very severe disability; 81–100% = completely disabled.

F. Neck Disability Index (NDI)

Scoring criteria:a. This scale assesses functional disability due to cervical spine disorders. It consists of 10 items covering various daily activities, each rated 0–5 (0 = no impact, 1 = mild impact, 2 = moderate impact, 3 = severe impact, 4 = extreme impact, 5 = unable to perform the activity). One answer is selected for each item, and scores are summed, yielding a raw total ranging from 0 to 50.b. The final score is expressed as a percentage: NDI (%) = (sum of item scores / 50) × 100%. Interpretation: 0–4 = no disability; 5–14 = mild disability; 15–24 = moderate disability; 25–34 = severe disability; ≥35 = complete disability.

G. Shoulder Pain and Disability Index (SPADI)

Scoring criteria:a. This scale assesses pain and functional disability due to shoulder disorders. It consists of two subscales: Pain (5 items) and Disability (8 items). Each item is rated 0–10 (0 = no pain/no limitation, 10 = extreme pain/unable to perform the activity).b. Pain subscore ranges from 0 to 50; Disability subscore ranges from 0 to 80. Total raw score ranges from 0 to 130. Percentage score: SPADI (%) = [(Pain score + Disability score) / 130] × 100%. Interpretation: 0–20% = mild pain and disability; 21–40% = moderate; 41–60% = severe; ≥61% = very severe.

H. American Orthopaedic Foot & Ankle Society Ankle-Hindfoot Scale (AOFAS-AH)

Scoring criteria:a. This scale assesses ankle and hindfoot function, consisting of three subscales: Pain (40 points), Function (50 points), and Alignment (10 points).b. Each item is scored according to graded criteria, and scores are summed for a total ranging from 0 to 100. Higher scores indicate better ankle-hindfoot function. Common grades: Pain (none = 40, mild = 30, moderate = 20, severe = 0); Alignment (good = 10, mild abnormality without symptoms = 5, obvious abnormality with symptoms = 0).

I. International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC)

Scoring criteria:a. This scale assesses knee function, covering symptoms, sports ability, and quality of life. It consists of two parts: Symptoms and Signs (e.g., pain, swelling) and Daily Activities and Sports Ability (e.g., walking, stair climbing, running). Each item is rated 0–4 (0 = no symptoms, 4 = extremely severe symptoms).b. Item scores are summed, and the total is transformed to a 0–100 scale. Higher scores indicate better knee function. Interpretation: 90–100 = normal knee function; 60–89 = mild dysfunction; 30–59 = moderate dysfunction; 0–29 = severe dysfunction.

J. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Scoring criteria:a. This scale assesses pain, stiffness, and physical function in osteoarthritis of the knee and hip. It consists of 24 items across three subscales: Pain (5 items), Stiffness (2 items), and Physical Function (17 items).b. Each item is rated 0–4 (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe).c. Subscale score ranges: Pain = 0–20; Stiffness = 0–8; Physical Function = 0–68. Total score = sum of all subscale scores. Interpretation: 0–20 = mild symptoms; 21–40 = moderate symptoms; 41–60 = severe symptoms; ≥61 = very severe symptoms.

K. Disabilities of the Arm, Shoulder and Hand Scale (DASH)

Scoring criteriaa. This scale assesses functional disability and symptoms due to disorders of the upper extremity (including shoulder, arm, hand, and fingers). It consists

of 30 items covering pain, daily activities, and motor ability. Each item is rated 0–4 (0 = no disability/symptoms, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe).b. Total score ranges from 0 to 100, with higher scores indicating greater upper extremity disability. Formula: DASH total score = (mean of all item scores) × 25. Interpretation: 0 = no disability; 1–20 = mild disability; 21–40 = moderate disability; 41–60 = severe disability; 61–100 = very severe disability.

The above scale assessments will be administered at the time points of MEG data acquisition.

3.9 Statistical Analysis Methods

Baseline MEG metrics and clinical data will serve as the primary predictive factors, with a focus on evaluating their predictive value for pain persistence and symptom improvement during follow-up. Given that treatment modalities and intensities may vary in real-world settings, treatment exposure information at each time point will be dynamically recorded and adjusted for in statistical analyses as time-fixed or time-varying covariates.

(1)Stratified/Subgroup Analyses: When sample size permits, analyses will be stratified by pain type, pain severity, disease duration, and major treatment pathways, with baseline MEG characteristics and predictive performance reported for each subgroup.

(2)Adjusted Analyses: Multivariate models will include covariates such as age, sex, BMI, disease duration, baseline scale scores, and treatment status/modality to evaluate the independent associations between MEG metrics and outcomes, without making causal inferences.

(3) For participants with repeated MEG or repeated outcome measurements, linear mixed-effects models, generalized estimating equations (GEE), or other statistical methods accounting for within-subject correlation will be used to avoid bias that may arise from treating repeated measurements as independent samples.

Descriptive statistics will be used to summarize baseline characteristics. For

baseline comparisons across different pain types, continuous variables will be analyzed using t-tests/ANOVA or rank-sum tests, and categorical variables using chi-square tests or Fisher's exact tests. Multivariate linear/logistic regression will be applied to adjust for confounders when necessary. For longitudinal outcome analyses, 6-month persistent pain status (VAS ≥ 3) and changes in VAS scores will serve as the primary outcomes. Multivariate logistic regression will be used to assess the association between baseline MEG and clinical characteristics and the risk of persistent pain. Linear mixed-effects models or GEE will be applied to analyze trends in VAS and other scale scores over time.

Predictive models will be developed based on baseline clinical data and MEG features, with data split chronologically or randomly at a 7:3 ratio into training and validation sets. Penalized regression or dimensionality reduction techniques will be applied to high-dimensional features to mitigate overfitting. Model performance will be evaluated using AUC with 95% CI, sensitivity, specificity, calibration curves, and Brier score. Bootstrap resampling will be used for internal validation. If independent samples are available, external validation and necessary model updating will be performed. For MEG comparisons across multiple brain regions and frequency bands, FDR or permutation methods will be used to control for multiple comparisons. Missing data will be described and, if necessary, handled using multiple imputation. A two-sided significance level of $\alpha = 0.05$ will be applied.

3.10 Quality Control

This study will be conducted in accordance with standardized protocols and operational procedures, covering the entire process including participant screening and enrollment, informed consent, clinical data and scale assessments, MEG examinations, data processing, and statistical analysis, to ensure consistency across all steps. Upon completion of each participant's examination, researchers will perform timely verification of key variables using a predefined checklist and implement closed-loop management (e.g., participant ID and group assignment, completeness of VAS and other scales, examination date and treatment status, MEG raw data file numbers and

coregistration information, etc.). Missing, abnormal, or logically inconsistent information will be traced, verified, corrected, and documented to ensure data traceability and auditability.

Before MEG acquisition, routine equipment status checks and magnetic shielding environment inspections will be conducted, and standardized acquisition parameters and procedures will be employed. After acquisition, basic data quality assessment will be performed, including signal-to-noise levels, artifacts (e.g., movement, electromyographic, or blink artifacts), task compliance, and data completeness. For data failing to meet quality standards, repeat acquisition will be prioritized when conditions permit. For cases where re-acquisition is not feasible, the reasons will be documented and the data will be handled according to predefined rules in subsequent analyses (e.g., exclusion or sensitivity analysis). All data will be de-identified using unique codes, and raw data, processed data, and analytical data will be stored at separate levels with regular backups.

4. Feasibility Analysis

This study is a single-center prospective cohort study. Pain participants will be continuously recruited from our hospital's outpatient clinics and inpatient wards, ensuring a stable source of study subjects. The hospital has an established routine follow-up process and an electronic medical record system, which facilitates the completion of follow-up assessments at 1 month, 3 months, and 6 months. Treatment status, medication use, and primary treatment modalities at each time point will be systematically documented to support longitudinal analyses.

Our institution is equipped with comprehensive MEG examination facilities and magnetic shielding environments, enabling on-site scheduling, data acquisition, and data management. MEG examination does not require contrast agent injection; the procedure is well-established and well-accepted by participants, facilitating its implementation during routine clinical care. Structural MRI will be used for coregistration with MEG data when available to improve the accuracy of brain region localization, which does not constitute a limitation to the conduct of this study.

The technical pathway is well-defined and operable. Baseline MEG data will undergo standardized preprocessing to extract neural oscillation and brain network features, including multi-band power spectra, functional connectivity, and relevant network metrics. These features will be integrated with baseline clinical phenotypes and follow-up outcomes to form a feature set for longitudinal statistical analyses and predictive modeling. Model development will employ clinically established and interpretable methods commonly used in clinical research, with feature selection or regularization applied as needed based on the actual sample size to mitigate overfitting risk. Internal validation will be performed using training/validation set splitting and bootstrap resampling, with AUC and calibration performance as the primary evaluation metrics.

Study data will be de-identified using unique coding, and clinical data along with MEG/imaging data will be uniformly archived with regular backups. Completeness and consistency checks will be performed after each data collection. Missing or anomalous data will be traced, corrected, and documented in a timely manner to ensure data traceability and process auditability. The study carries low and manageable overall risk and has a solid foundation for implementation.

5. Timeline

Study Milestone	Timeframe
Protocol finalization and ethical approval	January 2026 – May 2026
Continuous enrollment and data collection	May 2026 – December 2027
Data organization and quality control, MEG preprocessing/feature extraction	July 2026 – March 2028
Statistical analysis, model development and validation, manuscript writing and submission	March 2028 – December 2028

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Informed Consent Form for Pain Participants

Study Title: Study on Brain Network Characteristics of Pain Patients Based on Magnetoencephalography (MEG)

Principal Investigator: Wang Yonghui

Study Duration: May 26, 2026 – December 31, 2028

Planned Number of Participants: 1,000 participants

Name:_____

Sex:□ Male □ Female

Phone Number:_____

Mailing Address:_____

You are being invited to take part in a clinical research study. This informed consent document provides you with information that may help you decide whether or not to participate. Please read this document carefully. Should you have any questions, please do not hesitate to ask the study physician responsible for this research.

(I) **Study Content and Study Purpose**

This study employs magnetoencephalography (MEG) as the core assessment tool. MEG measurements will be performed within a magnetic shielding device under an ultra-weak magnetic environment approaching zero magnetic field, using atomic spin magnetometers to measure and record the weak magnetic field signals naturally generated by neural electrical activity of the brain, thereby obtaining key parameters such as neural oscillations and functional connectivity of brain networks. The study plans to recruit both healthy volunteers and pain participants, and to collect necessary clinical information as well as scale-based data on pain, mood, sleep, and function. Structural MRI will be coregistered with MEG data where available to improve the accuracy of brain region localization. By comparing differences in MEG-derived neural oscillations and functional connectivity between pain

participants and healthy controls, as well as among subgroups with different treatment statuses or modalities, and by analyzing their associations with pain intensity, disease duration, and related clinical phenotypes, this study aims to identify reproducible pain-related abnormal brain network patterns, screen candidate objective neural biomarkers, and provide a basis for subsequent efficacy evaluation and longitudinal follow-up or interventional studies.

(II) **Study Design**

This study is a single-center, prospective clinical study that plans to recruit pain participants. If you agree to participate, the researcher will first conduct a screening assessment to confirm whether you meet the inclusion/exclusion criteria. Please provide truthful information regarding your basic personal details, medical history, and recent medication use, and cooperate with the completion of the informed consent process.

After enrollment, you will undergo a magnetoencephalography (MEG) examination at a scheduled appointment. Where available, cranial MRI may be performed for coregistration with MEG data to improve the accuracy of brain region localization. The MEG examination must be completed within a magnetic shielding device. It is a non-contact, non-invasive procedure that does not require contrast agent injection. The total experimental paradigm duration is approximately 10 minutes (including working memory tasks, eyes-open/eyes-closed resting-state measurements, and stimulation-evoked measurements).

Before the examination, please carefully read the relevant precautions, remove all metal objects and items that may affect the examination, wear clothing without metal accessories, and cooperate with the examination procedures. The study will collect your clinical data and questionnaire-based assessments, which will be analyzed in conjunction with MEG data. This study does not involve blood sample collection. All study data will be de-identified using coded identifiers.

(III) **Institutional Qualifications:**

Our institution is a Class A Tertiary hospital capable of conducting standardized,

high-quality clinical research in pain and related fields.

(IV) **Risks and Discomforts:**

This study involves certain examinations that may entail the following risks and discomforts:

1. Magnetoencephalography (MEG) is a non-contact, non-invasive, and rapid detection method. However, a small number of participants may experience unforeseeable risks or complications due to idiosyncratic physical conditions or factors that cannot be detected by current medical techniques.
2. This study does not recommend MEG examination for individuals with claustrophobia, unstable asthma, or those who are pregnant. Please fully and promptly inform the medical staff of any relevant medical history or conditions to facilitate a thorough risk assessment.
3. Most metals can affect the accuracy of MEG results, while certain non-magnetic metals of special materials have minimal impact. Please proactively inform the medical staff whether you have any history of internal implants, including but not limited to pacemakers, prosthetic heart valves, insulin pumps, cochlear implants, drug infusion pumps, endovascular stents, catheters, dentures, or artificial eyes, and cooperate with the medical staff by providing relevant documentation or explanations.
4. Participants with acute, critical, or severe illnesses generally face higher risks during examinations. Such conditions include but are not limited to aortic dissection aneurysm, pulmonary embolism, severe cardiac, hepatic, or renal insufficiency, and pulmonary hypertension. Please inform the medical staff of any such medical history in advance.
5. Cranial MRI examination typically lasts approximately 10 minutes.

(V) **Costs of Participation:**

All study-related examinations and procedures will be provided at no cost to you. You will not be charged any additional fees for participating in this study.

(VI) **Your Rights and Responsibilities:**

Rights:

1. **Confidentiality:** If you decide to participate, your personal information will be strictly protected. All data will be coded with a study number rather than your name. Your identifying information will not be disclosed to anyone outside the research team without your consent. All researchers are obligated to keep your identity confidential. Your records will be stored in locked cabinets accessible only to authorized research personnel. Study findings may be published in scientific journals, but no personal information such as your name or address will be disclosed.

2. **Voluntary participation:** Your participation is entirely voluntary. You may refuse to participate or withdraw at any time by notifying the study physician. Should you withdraw, your data will be excluded from the final analysis, and your medical care and legal rights will not be compromised.

Responsibilities:

1. Provide accurate and complete information about your personal background, medical history, and treatment history to facilitate the study.

2. Follow the study physician's instructions and complete all required examinations as scheduled.

3. Carefully review and understand all examination precautions, potential risks, unexpected events, and unforeseeable circumstances.

4. Consent to the physician's adjustments to the examination protocol based on your condition during the examination. In the event of any risk or emergency, you authorize the medical staff to provide treatment in accordance with standard medical procedures.

(VII) **Benefits:**

Through magnetoencephalography (MEG) examination, weak magnetic signals generated by neural electrical activity of the brain can be recorded in a non-invasive, radiation-free manner, reflecting cerebral neural activity and brain network status at the functional level. In some cases, MEG may provide supplementary information regarding brain functional abnormalities that are not readily detectable by

conventional structural imaging. Participation in this study entitles you to receive the relevant examinations free of charge, as well as corresponding health guidance and recommendations. In addition, after completing the study, participants will be eligible to receive two additional sessions of free routine treatment, with the specific treatment modalities to be arranged according to individual circumstances.

(VIII)

If you have any further questions regarding this study, please contact the study physician or designated research staff using the contact information provided below:

- **Study Physician:** Xiangxin Xing **Phone:**86-18560086949
- **Designated Research Staff:**Xiaofei Zhang **Phone:**86-15563139097

(IX)

I have accurately explained this informed consent document to the study participant. The participant has read and understood the information provided, and I confirm that he/she was afforded the opportunity to ask questions. I hereby confirm that the participant has provided consent voluntarily.

Investigator Signature:_____

Date:_____ Year _____ Month _____ Day

(X)

I have read and understood all the information provided above. The Principal Investigator/Investigator has fully addressed all my questions concerning the study plan. Having fully comprehended the details of this research and after due consideration, I hereby voluntarily consent to participate as a participant in this clinical study.

Participant Signature:_____

Date:_____ Year _____ Month _____ Day

Informed Consent Form for Healthy Participants

Study Title: Study on Brain Network Characteristics of Pain Patients Based on Magnetoencephalography (MEG)

Principal Investigator: Wang Yonghui

Study Duration: May 26, 2026 – December 31, 2028

Planned Number of Participants: 1,000 participants

Name:_____

Sex:□ Male □ Female

Phone Number:_____

Mailing Address:_____

You are being invited to take part in a clinical research study. This informed consent document provides you with information that may help you decide whether or not to participate. Please read this document carefully. Should you have any questions, please do not hesitate to ask the study physician responsible for this research.

(I) **Study Content and Study Purpose:**

This study utilizes a domestically developed magnetoencephalography (MEG) device to non-invasively, efficiently, and conveniently capture the weak magnetic signals generated by human brain tissue, with the goal of establishing normative reference ranges for key MEG parameters. MEG recordings are performed within a magnetically shielded room, using optically pumped atomic magnetometers to measure the magnetic fields naturally produced by the brain's electrical activity in an ultra-low magnetic field environment approaching zero field. The MEG procedure requires no contrast agent injection and is a non-contact, non-invasive, and rapid technique for evaluating cerebrovascular conditions.

Healthy participants will be recruited for this study. All enrolled individuals will undergo MEG examinations and provide clinical information (including sex, age, and

medical history). Cranial MRI will be performed when deemed necessary.

(II) **Study Design:**

This is a prospective clinical study recruiting healthy participants. If you agree to take part, the study physician will perform a screening evaluation to determine your eligibility. Please provide accurate and complete information about your personal background and medical history.

You will undergo MEG examinations at no cost. MEG is a non-invasive, radiation-free functional assessment of the brain that poses no trauma or harm to your body.

Prior to the MEG examination, please carefully review the precautions and the potential risks and discomforts. On the day of the examination, please remove all metal objects and magnetically sensitive items from your person, and wear clothing without metal zippers, buttons, or underwire. Also remove any medicated patches, metal jewelry, or undergarments containing metal within the scan area as instructed. Clinical information will be collected, and MEG data will be used for subsequent analyses. No blood samples will be collected in this study.

(III) **Institutional Qualifications:**

Our institution is a Class A Tertiary hospital capable of conducting standardized, high-quality clinical research in pain and related fields.

(IV) **Risks and Discomforts:**

This study involves certain examinations that may entail the following risks and discomforts:

6. Magnetoencephalography (MEG) is a non-contact, non-invasive, and rapid detection method. However, a small number of participants may experience unforeseeable risks or complications due to idiosyncratic physical conditions or factors that cannot be detected by current medical techniques.
7. This study does not recommend MEG examination for individuals with claustrophobia, unstable asthma, or those who are pregnant. Please fully and

promptly inform the medical staff of any relevant medical history or conditions to facilitate a thorough risk assessment.

8. Most metals can affect the accuracy of MEG results, while certain non-magnetic metals of special materials have minimal impact. Please proactively inform the medical staff whether you have any history of internal implants, including but not limited to pacemakers, prosthetic heart valves, insulin pumps, cochlear implants, drug infusion pumps, endovascular stents, catheters, dentures, or artificial eyes, and cooperate with the medical staff by providing relevant documentation or explanations.
9. Participants with acute, critical, or severe illnesses generally face higher risks during examinations. Such conditions include but are not limited to aortic dissection aneurysm, pulmonary embolism, severe cardiac, hepatic, or renal insufficiency, and pulmonary hypertension. Please inform the medical staff of any such medical history in advance.
10. Cranial MRI examination typically lasts approximately 10 minutes.

(V) Benefits:

Following study evaluation and with your informed consent, you will receive a free MEG examination as a healthy participant. When available and deemed necessary, supplementary cranial structural MRI may be performed to facilitate coregistration with MEG data and enhance anatomical localization accuracy; all associated costs will be covered by this study.

Based on health questionnaires/scale assessments and the above examinations, you will receive free health guidance and recommendations concerning sleep, emotional well-being, and lifestyle. If any significant abnormalities are detected that require clinical attention, the research team will notify you in a timely manner and suggest a referral to the relevant specialty for further assessment (please note that research examinations are not a substitute for clinical diagnosis).

Your involvement will contribute to establishing normative MEG baseline reference values and key parameter ranges in healthy individuals, which will serve as a critical benchmark for future comparisons with pain patients, investigations of

pain-related brain network characteristics and therapeutic impacts, and the advancement of standardized clinical applications and translation of MEG technology.

After completing the full study protocol, you will be offered a complimentary health evaluation. Additionally, two sessions of personalized rehabilitation guidance may be provided if you so desire.

(VI) **Costs of Participation:**

All study-related examinations and procedures will be provided at no cost to you. You will not be charged any additional fees for participating in this study.

(VII) **Your Rights and Responsibilities:**

Rights:

1. **Confidentiality:** If you decide to participate, your personal information will be strictly protected. All data will be coded with a study number rather than your name. Your identifying information will not be disclosed to anyone outside the research team without your consent. All researchers are obligated to keep your identity confidential. Your records will be stored in locked cabinets accessible only to authorized research personnel. Study findings may be published in scientific journals, but no personal information such as your name or address will be disclosed.
2. **Voluntary participation:** Your participation is entirely voluntary. You may refuse to participate or withdraw at any time by notifying the study physician. Should you withdraw, your data will be excluded from the final analysis, and your medical care and legal rights will not be compromised.

Responsibilities:

1. Provide accurate and complete information about your personal background, medical history, and treatment history to facilitate the study.
2. Follow the study physician's instructions and complete all required examinations as scheduled.
3. Carefully review and understand all examination precautions, potential risks,

unexpected events, and unforeseeable circumstances.

4. Consent to the physician's adjustments to the examination protocol based on your condition during the examination. In the event of any risk or emergency, you authorize the medical staff to provide treatment in accordance with standard medical procedures.

(VIII)

If you have any further questions regarding this study, please contact the study physician or designated research staff using the contact information provided below:

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Investigator Signature:_____

Date:_____ Year _____ Month _____ Day

(X)

I have read and understood all the information provided above. The Principal Investigator/Investigator has fully addressed all my questions concerning the study plan. Having fully comprehended the details of this research and after due consideration, I hereby voluntarily consent to participate as a participant in this clinical study.

Participant Signature:_____

Date:_____ Year _____ Month _____ Day