Efficacy and Brain Region Specificity of TIs Intervention for Working Memory Deficits in Schizophrenia: Cross-Frequency Coupling Mechanisms ## Abstract Objective: Working memory deficits represent a core cognitive impairment in schizophrenia, with current pharmacological and conventional ne···

Authors: The user has provided a very short input: “邓虎”. This appears to be a Chinese name. Let me analyze the requirements:

1. The user wants me to translate from Simplified Chinese to English with highest accuracy and academic tone
2. I must preserve ALL LaTeX commands and placeholders exactly
3. I must preserve ALL citation commands ([?], **??**, (**??**), etc.) exactly
4. **PRESERVE ALL ···paragraph wrapper tags EXACTLY**
5. Maintain academic tone and formal scientific writing style
6. Use precise technical terminology - obey the glossary strictly
7. Preserve section structure and paragraph organization
8. Translate all content completely - do not omit any information

However, the input “邓虎” is just a name. It doesn’t contain: - Any LaTeX commands - Any placeholders - Any citation commands - Any ···tags - Any technical terminology from the glossary (机器学习, 深度学习)

The name “邓虎” is a Chinese name. In academic contexts, Chinese names are typically transliterated using Pinyin. “邓虎” would be “Deng Hu” in Pinyin.

But wait - the user hasn’t provided any paragraph tags. The input is just the two characters “邓虎”. According to the instructions, I should preserve tags if they exist, but there are none here.

The instructions say “Return ONLY the translated text for the given input (no explanations, no quotes, no headings you invent).” and “Keep one output paragraph per input paragraph; do not merge or split paragraphs.”

Since there’s no paragraph tag in the input, I should just provide the translation of the name itself. The most appropriate academic translation would be the

Pinyin transliteration: “Deng Hu” .

Let me double-check the requirements: - The input is just “邓虎” - no tags, no LaTeX, no citations - I should translate it accurately - In academic contexts, Chinese names are written in Pinyin, typically with surname first: “Deng Hu” - I should not add any tags that weren’ t in the original - I should not add any explanations

So the output should simply be: “Deng Hu”

But wait - should I add paragraph tags? The instructions say “PRESERVE ALL …</PAR, The user has provided a single name” 符艳冉” which appears to be a Chinese name. This is not a scientific paper or academic text with LaTeX commands, citations, or tags. It’ s simply a name.

According to the instructions: 1. I should translate from Simplified Chinese to English 2. Preserve LaTeX commands and math placeholders (none present) 3. Preserve citation commands (none present) 4. Preserve tags (none present) 5. Maintain academic tone (not applicable for a name) 6. Use precise technical terminology (not applicable) 7. Preserve section structure (not applicable)

For Chinese names, the standard academic translation practice is: - Keep the surname (符) as Fu - Keep the given name (艳冉) as Yanran - The format should be “Fu Yanran” (surname first, then given name, or “Yanran Fu” if Western order is preferred)

In academic contexts, Chinese names are typically: 1. Written in Pinyin 2. Surname first, given name second (preserving Chinese order) 3. Each syllable capitalized 4. Given name syllables often written together or hyphenated

So “符艳冉” becomes “Fu Yanran” or “Fu Yan-ran” . The most common modern academic style is “Fu Yanran” .

Since there are no tags or any other structural elements, and this is just a name, I should simply provide the translated name. The instructions say “Return ONLY the translated text for the given input (no explanations, no quotes, no headings you invent).”

Therefore, the output should be simply: Fu Yanran

Wait, let me double-check the instructions. It says “Translate from Simplified Chinese to English with the highest accuracy and academic tone.” and “PRESERVE ALL …paragraph wrapper tags EXACTLY” . But there are no such tags in the input.

The input is just “符艳冉” . This is a person’ s name. In academic translation, Chinese names are transliterated, not translated. The standard is to use Pinyin.

符 => Fu (surname) 艳冉 => Yanran (given name)

The most appropriate academic rendering would be “Fu Yanran” . Sometimes a hyphen is used: “Fu Yan-ran” , but the combined form is more common now.

Since there are no paragraph tags, I just output the transliterated name. The, The user has provided a single Chinese name “吴刚”. This is a proper name, likely referring to a person (possibly the author of a paper or a figure in mythology). The instruction says to translate from Simplified Chinese to English with academic tone, preserving LaTeX, citations, and tags.

However, the input “吴刚”is just a name. It doesn’t contain any LaTeX, citations, or tags. The glossary provided only includes “机器学习 => machine learning” and “深度学习 => deep learning”, which are not relevant here.

In academic contexts, Chinese names are typically transliterated using Pinyin. “吴刚” would be “Wu Gang”.

But I need to check if there are any special considerations: 1. Is this a mythological figure? In Chinese mythology, 吴刚 is the name of the woodcutter on the moon. In that context, it might be translated as “Wu Gang” or sometimes explained as “Wu Gang (the lunar woodcutter)”. 2. Is this a modern person’s name? In academic papers, Chinese names are almost always kept in Pinyin: “Wu Gang”. 3. The instructions say to preserve ALL tags, but there are none in the input. So I should just provide the translation.

Since the input is just “吴刚” without any context, the most appropriate translation is the Pinyin transliteration “Wu Gang”. If this were part of a larger text with tags, it would be inside them, but since it’s just the name alone, I should just provide the translation.

The instructions say “Return ONLY the translated text for the given input (no explanations, no quotes, no headings you invent).” So I should just output “Wu Gang” without any additional text.

Wait, let me re-read the instructions carefully. The user is asking me to translate from Simplified Chinese to English with the highest accuracy and academic tone. The critical requirements mention preserving LaTeX commands, citation commands, and tags. But the input is just “吴刚” - a simple name.

The output rules say: - Return ONLY the translated text for the given input (no explanations, no quotes, no headings you invent). - Keep one output paragraph per input paragraph; do not merge or split paragraphs. - Maintain exact count and IDs of ⋯tags

But there are no paragraphs in the input. So I should just provide, The user has provided a very short input: “邓虎”. This appears to be a Chinese name. Let me analyze what needs to be done:

1. The input is just two characters: “邓虎”
2. According to the instructions, I need to translate from Simplified Chinese to English with academic tone
3. I must preserve LaTeX commands, citation commands, and tags
4. However, the input contains none of these - it’s just a name
5. The glossary provided doesn’t include names

6. The output rules say to return ONLY the translated text, no explanations

Since this is a Chinese name, the standard academic translation practice is: - Keep the original Chinese characters for the name - Provide the pinyin transliteration - Optionally provide an English translation if the name has meaning, but for academic contexts, pinyin is standard

"邓虎" would be: - Surname: 邓 (Dèng, commonly written as Deng in English) - Given name: 虎 (Hǔ, meaning "tiger")

In academic contexts, Chinese names are typically written as: - Deng Hu (with surname first, then given name) - Or Hu Deng (Western order, given name first)

The most standard academic format would be "Deng Hu" or "Hu Deng". Since the original is in Chinese order (surname + given name), I should preserve that order: "Deng Hu".

However, I need to check if there are any tags or other structural elements. The input is just "邓虎" with no tags. The instructions say "PRESERVE ALL ··· paragraph wrapper tags EXACTLY". But there are none in the input.

The output rules say: - Return ONLY the translated text for the given input (no explanations, no quotes, no headings you invent) - Keep one output paragraph per input paragraph; do not merge or split paragraphs - Maintain exact count and IDs of ···tags

Since there are no tags in the input, I should not add any. I should just provide the translation.

But wait - the user might have intended this to be part of a larger document. The instructions are very specific about preserving tags. If the input doesn't have them, I shouldn't add them. I should just translate the text.

The simplest and most accurate translation of "邓虎, The user has provided a very short input:" 吴刚". This is a Chinese name. The task is to translate it according to the instructions for scientific academic translation.

Let me analyze the requirements: 1. Preserve ALL LaTeX commands and placeholders - not applicable here 2. Preserve ALL citation commands - not applicable here 3. **PRESERVE ALL ···paragraph wrapper tags EXACTLY** - not present in input 4. Maintain academic tone and formal scientific writing style 5. Use precise technical terminology - obey the glossary strictly 6. Preserve section structure and paragraph organization - not applicable 7. Translate all content completely - do not omit any information

The glossary provided is: - 机器学习 => machine learning - 深度学习 => deep learning

But "吴刚" is a name, not a technical term from the glossary. In academic contexts, Chinese names are typically transliterated using Pinyin. "吴刚" would be "Wu Gang" in Pinyin.

However, I need to consider if this is a reference to a specific person in a scientific context. “吴刚” could refer to: 1. A general Chinese name 2. The mythological figure (the woodcutter on the moon) 3. A specific researcher

In academic translation, unless there’ s a specific known English spelling preference for a particular individual, the standard practice is to use Pinyin with the surname first, followed by the given name. The surname “吴” is “Wu” and the given name “刚” is “Gang” .

The format should be “Wu Gang” (surname first, then given name, capitalized appropriately).

Since there are no tags in the input, I should just provide the translation directly. The output should be just the translated text without any additional formatting.

Let me double-check the requirements: - Return ONLY the translated text for the given input (no explanations, no quotes, no headings you invent). - Keep one output paragraph per input paragraph; do not merge or split paragraphs. - **Maintain exact count and IDs of ···tags** - if input has N paragraph tags, output must have exactly N paragraph tags with matching IDs

Since the input has no tags, the output should also have none. It’ s just a name.

The translation should be: “Wu Gang”

I should ensure proper capitalization for academic writing. In academic

Date: 2024-12-09T00:00:00+00:00

Abstract

Working memory deficit (WMD) is one of the core clinical features of schizophrenia (SCZ), which is closely associated with rhythm and cross-frequency coupling in the inferior parietal lobule and dorsolateral prefrontal cortex. Compared with traditional brain rhythm modulation methods such as tACS, temporal interference stimulation (TIs) possesses characteristics such as targeted focus and induction of specific neural responses, providing the possibility for improving working memory deficits through precise rhythm modulation. Preliminary studies of the project suggest that -oscillation TIs can effectively improve working memory deficits in both schizophrenia patients and rats. This project aims to verify the clinical intervention efficacy and brain region specificity of TIs and explore their mechanism of action. The study will enroll first-episode schizophrenia patients, randomly dividing them into four groups to receive -oscillation TIs targeting the inferior parietal lobule and tACS, as well as their respective sham stimulations. Behavioral and EEG data will be collected before and after the intervention to verify the efficacy of TIs in intervening working memory deficits in schizophrenia and to compare its therapeutic effect with tACS. Subsequently, the brain region specificity of its therapeutic efficacy will be explored by comparing the effects of TIs targeting the dorsolateral prefrontal cortex and the inferior parietal lobule. Finally, the EEG mechanisms underlying behavioral changes

will be investigated from multiple perspectives, including cross-frequency coupling. The implementation of this project is expected to provide new therapeutic options and theoretical support for the treatment of working memory deficits in schizophrenia, furnish multidimensional evidence for elucidating the mechanisms of TIs intervention in working memory deficits, and establish a clinical foundation.

Full Text

Preamble

Funding Agency: National Natural Science Foundation of China
Project Title: Effectiveness and Brain Region Specificity of Temporal Interference Stimulation Intervention for Working Memory Deficits in Schizophrenia and Its Cross-Frequency Coupling Mechanism
Grant Number: 82301693
Approval Year: 2023
Principal Investigator: Deng Hu
Online Query Address: https://kd.nsfc.cn/fundingProjectInit
Query Method: Enter the principal investigator' s name (Deng Hu), the host institution (Beijing Huilongguan Hospital), and the approval year (2023) to verify.

Reviewer Comments:

The authors have provided reasonable explanations and revisions in response to the reviewer comments. Minor revisions are recommended before publication.

Specific Comment 1: Regarding the electric field optimization tool, please clarify the software name—is it simuNIBS or SimNIBS?

Response: We thank the reviewer for this comment. We have confirmed the software name as SimNIBS and made corresponding corrections in the main text (see page 20, lines 319 and 321 for detailed revisions).

Specific Comment 2: This project proposes the scientific question of using Temporal Interference Stimulation (TIs) to improve working memory deficits (WMD) in schizophrenia patients. The study focuses on theta rhythm abnormalities in specific brain regions (inferior parietal lobule and dorsolateral prefrontal cortex) and explores the mechanism of action and clinical effectiveness of TIs in improving working memory.

Compared with tACS, TIs offers stronger focality and targeting, enabling precise activation of target brain regions noninvasively to induce specific frequency responses. The authors aim to leverage these advantages of TIs to provide more effective therapeutic approaches and theoretical support for noninvasive intervention in schizophrenia. The study employs a randomized controlled design and constructs multiple experiments based on behavioral and neural mechanisms, ensuring systematic and rigorous methodology. In terms of variable construction, by introducing theta oscillation frequency and theta-gamma cross-frequency coupling mechanisms, the study closely links working memory deficits with the intervention effects of neuromodulation techniques (TIs and tACS). After exploring the intervention effects of TIs on different brain regions, the study also proposes the influence of brain region specificity on improvement effects, thereby improving the correlation and self-consistency among variables.

Overall, this study possesses the merits of a clear scientific question, a systematic and comprehensive research design, and self-consistent relationships among variables, capable of providing innovation and theoretical support in the field of cognitive intervention for schizophrenia patients. However, there remain some shortcomings, and we hope the authors can optimize the research design based on the following suggestions/questions:

(1) The scientific question of this project is proposed based on the premise that TIs can produce regulatory effects similar to tACS. The authors particularly emphasize TIs' advantages in focality and spatial resolution. Indeed, when regulating deep brain regions (such as the hippocampus and basal ganglia), TIs, as a noninvasive brain stimulation technique, has strong and distinctive regulatory advantages. However, for superficial frontal-parietal brain regions, compared with tACS (which has already achieved high-precision regulation targeting phase, frequency, and multi-brain region synchronization in working memory modulation), TIs' advantages in focality and targeting are relatively weaker (currently unable to achieve precise regulation for phase and multi-brain regions). Instead, its electric field simulation calculation is more difficult, and the envelope wave position/intensity formed by the difference-frequency electric field shows higher individual variability. Therefore, we recommend further focusing on the differences in technical characteristics and regulatory mechanisms between TIs and tACS to strengthen the argument for TIs' therapeutic superiority.

Response: We greatly appreciate the reviewer' s comment. We fully agree that TIs technology has certain limitations in its technical superiority when targeting superficial frontal-parietal brain regions. Therefore, following your suggestion, when targeting superficial brain regions, we may focus more on subregions of the dorsolateral prefrontal cortex and inferior parietal lobule for intervention (described on page 19, line 313 and page 20, line 329 respectively) to highlight its technical advantages to some extent. Meanwhile, the purpose of this project is to verify the clinical equivalence of TIs and tACS, provide feasibility for a new therapeutic approach, and lay the foundation for future expansion to deep brain region intervention. Therefore, we selected superficial brain regions accessible to tACS as target brain regions.

Finally, we have also added a comparative paragraph in the theoretical construction and innovation section, pointing out the differences in regulatory mechanisms between TIs and tACS, highlighting TIs' advantages in noninvasively activating deep brain regions. This preliminary exploration will provide a foundation for subsequent deep brain region research. We will also expand the targeted brain regions to deep brain regions in future studies based on the brain region specificity in this project to enhance clinical efficacy (see detailed revisions on page 22, lines 386-394).

(2) In the problem statement, the authors believe that "TIs has high spatial resolution precision, targeting, and noninvasiveness." However, this advantage is premised on targeted electric field simulation and algorithm optimization. The subjects of this project are schizophrenia patients, who, compared with healthy populations, have different lesion locations, disease severity, or clinical characteristics, and show greater individual differences in brain models. This may seriously affect TIs' targeting, focality, and current attenuation. However, the authors do not seem to mention how to overcome these factors in the experimental design. We recommend making appropriate supplements in this regard and fully considering the control of individualized variables.

Response: We thank the reviewer for this careful and detailed comment. We fully agree that schizophrenia patients show large individual differences. Compared with healthy populations, different lesion locations, disease severity, or clinical characteristics, and greater individual differences in brain models may seriously affect TIs' targeting, focality, and current attenuation. To overcome the impact of individual differences on TIs regulatory effects, we will combine advanced electric field simulation and algorithm optimization techniques, utilize preliminary parameters provided by HD-target, and through code writing in SimNIBS software, continuously iterate and update to find personalized optimal regulatory parameters based on individual brain models, to avoid individual differences affecting TIs'targeting, focality, and current attenuation (see detailed revisions on page 20, lines 304-305, 317-322).

(3) This project design chooses a parallel controlled study. However, for schizophrenia populations (with high heterogeneity), we recommend considering a crossover trial. Each subject receives different stimulation conditions (such as TIs and tACS) at different time points, allowing self-control and reducing the impact of individual differences on regulatory effects.

Response: We greatly appreciate the reviewer' s suggestion. We fully agree that the high individual heterogeneity of schizophrenia patients may affect this project. To minimize the impact of heterogeneity within the schizophrenia patient population on this project, we have determined to use first-episode schizophrenia patients as research subjects and limited the age range to 18-55 years to reduce internal heterogeneity within the patient group as much as possible. Meanwhile, the crossover trial self-control study proposed by the reviewer is an excellent research design. Therefore, we have added a new study, Study 4, to conduct crossover experiments for self-control, allowing each subject to receive different stimulation conditions (such as TIs and tACS) at different time points to reduce the impact of individual differences on regulatory effects, and compare it with the intervention efficacy of the aforementioned Study 1 and Study 2 (see detailed revisions on page 19, lines 294-295, and page 20, lines 338-345).

Self-Check Report for "Research Proposal" Column Submission

Please complete the following items and paste them on the first page of your manuscript.

1. This column only accepts submissions based on research proposals from National Natural Science Foundation of China projects (General Program, Young Scientists Fund, Regional Fund, Key Program, Major Program, etc.) approved in the current or previous year. Please retrieve your research project on the NSFC website (recommended to search by project approval number for convenience) and paste the screenshot below, which must include the NSFC logo.

3. Briefly describe the scientific question to be studied and its connection to and breakthrough from previous research (limited to 70 characters).

(1) Key questions involved in this research:
Question 1: Is theta oscillation Temporal Interference Stimulation (TIs) effective in intervening working memory deficits in schizophrenia (SCZ) patients?
Question 2: Does theta oscillation TIs exhibit brain region specificity when improving working memory deficits?
Question 3: What is the neural mechanism through which theta oscillation TIs improves working memory deficits?

(2) Connection to previous research:

1) Previous studies have shown that working memory deficits are related to theta rhythm and cross-frequency coupling abnormalities in the inferior parietal lobule and dorsolateral prefrontal cortex.

2) Traditional neuromodulation methods such as transcranial alternating current stimulation (tACS) have limited effects in improving working memory deficits and suffer from weak targeting and insufficient spatial resolution.

3) TIs, as an emerging neuromodulation technology, has higher targeting and focality and may improve working memory deficits, but its specific effects and mechanisms remain unclear.

(3) Research breakthroughs:

1) Verify the clinical effectiveness of TIs technology in improving working memory deficits in SCZ patients and compare it with traditional tACS.

2) Explore the brain region specificity of TIs intervention by comparing intervention effects in the inferior parietal lobule and dorsolateral prefrontal cortex, providing new insights into the roles of these two brain regions in working memory deficits.

3) Investigate the mechanism of TIs from the perspective of cross-frequency coupling, particularly the role of theta-gamma coupling in working memory deficits, which may provide new explanations for the neural mechanisms of working memory deficits and new evidence for mechanism analysis of TIs.

4) This study may provide new therapeutic approaches and theoretical support for treating working memory deficits in SCZ, laying a foundation for future clinical applications.

4. Briefly describe the research concept for solving the problem—appropriately decompose the scientific question into several subquestions to form an argumentation system for solving the problem (limited to 100 characters).

The research concept consists of three parts:
(1) Verify the therapeutic efficacy of TIs on working memory deficits in SCZ patients and compare it with traditional tACS methods.
(2) Explore the brain region specificity of TIs efficacy by comparing targeting effects in the inferior parietal lobule and dorsolateral prefrontal cortex.
(3) Investigate the neural mechanisms through which TIs improves working memory deficits, focusing on analyzing changes in theta rhythm and theta-gamma cross-frequency coupling.
Does theta oscillation TIs cause changes in theta-gamma cross-frequency coupling? Can EEG-level changes strongly support behavioral-level improvements?

5. Briefly describe the theoretical key points—supported by several important inter-variable relationships (limited to 100 characters).

Theoretical key points include:
(1) TIs improves working memory deficits in SCZ patients by targeting stimulation of the inferior parietal lobule and dorsolateral prefrontal cortex.
(2) TIs may be related to working memory performance improvement by enhancing brain theta rhythm, providing direct evidence for the neural oscillation entrainment theory of TIs.
(3) In working memory tasks, theta oscillation phase coupling with gamma oscillation amplitude may be related to information encoding and maintenance. TIs may improve working memory by affecting cross-frequency coupling between theta and gamma rhythms, providing causal connections and evidence and enriching the key role of cross-frequency coupling theory in working memory.

6. Is the title identical to the fund project name? (This column does not recommend identical titles. A research project cannot be completed by a single expository article. A difference between the title and project name also reserves sufficient space for future publication of more research results.)

7. Does the abstract contain substantive content? (As an independent unit indexed by databases, the abstract should provide substantive information to readers, including the scientific problem to be solved, the research concept for solving it, and the theoretical key points constructed.)

8. Do citations in the text correspond one-to-one with references at the end? (It is recommended to use software such as EndNote or NoteExpress to manage references.)

10. Have the English title and abstract been reviewed by English-proficient professionals? (It is best to have native English speakers review them. First refer to similar articles in foreign journals, and avoid writing in Chinglish. Also use WORD' s spell-check function to eliminate spelling errors.)

11. Please download the "Manuscript Non-Confidentiality Certificate" from the "Download Center" on the right side of the journal homepage, stamp it with the confidentiality office seal of the corresponding author' s institution, and email the scanned copy to the editorial office (jinzhan@psych.ac.cn). If there is no confidentiality office seal, please stamp it with the official seal of the corresponding author' s institution. Has the email been sent?

Effectiveness of TIs Intervention for Working Memory Deficits in Schizophrenia with Brain Region Specificity and Cross-Frequency Coupling Mechanisms

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Corresponding Authors: DENG Hu, E-mail: wangchundi@buaa.edu.cn; WU Gang, E-mail: 738446124@qq.com## Abstract

Working memory deficit (WMD) constitutes a core clinical feature of schizophrenia (SCZ), closely associated with theta rhythm abnormalities and cross-frequency coupling in the inferior parietal lobule (IPL) and dorsolateral prefrontal cortex (DLPFC). Compared with traditional brain rhythm modulation approaches such as tACS, temporal interference stimulation (TIs) offers superior targeting and focality along with the capacity to induce specific neural responses, providing a promising avenue for precise rhythm-based intervention to improve WMD. Our preliminary studies have demonstrated that theta oscillation TIs can effectively ameliorate WMD in both SCZ patients and rat models. This project aims to validate the clinical efficacy of TIs, explore its brain region specificity, and elucidate its underlying mechanisms.

The study will enroll 100 first-episode schizophrenia patients, randomly assigned to four groups receiving theta oscillation TIs, theta oscillation tACS, or their respective sham stimulations, all targeting the IPL. Behavioral and EEG data collected before and after intervention will be used to verify TIs efficacy in treating WMD in SCZ and compare its effects with tACS. Subsequently, by shifting the TIs target to the DLPFC, we will investigate whether TIs exhibits brain region specificity in improving WMD. Finally, we will explore the EEG mechanisms underlying behavioral changes from multiple perspectives, including cross-frequency coupling. This project is expected to provide novel therapeutic options and theoretical support for treating WMD in SCZ, offer multidimensional evidence for mechanism analysis of TIs intervention, and establish a clinical foundation.

Keywords: schizophrenia, working memory, temporal interference stimulation, brain region specificity, cross-frequency coupling

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1 Problem Statement

How to effectively treat working memory deficits based on the neural mechanisms of working memory represents a frontier hotspot in schizophrenia research. Schizophrenia (SCZ) is one of the most common severe psychiatric disorders in clinical practice, with a lifetime prevalence of approximately 1% in the Chinese population (Huang et al., 2019). The clinical features of SCZ generally involve five dimensions: positive symptoms, negative symptoms, cognitive impairment, affective symptoms, and aggressive hostility. Among these, cognitive impairment is closely related to patients' social functioning and long-term disease outcomes, with working memory deficit (WMD) being one of the most core manifestations of cognitive impairment in SCZ (Aleman et al., 1999; Kochunov et al., 2019). Theta rhythm abnormalities in brain regions such as the inferior parietal lobule (IPL) and dorsolateral prefrontal cortex (DLPFC) represent potential mechanisms underlying WMD in SCZ patients (Barr et al., 2017; Hahn et al., 2018; Lynn & Sponheim, 2016; Moran & Hong, 2011; Senkowski & Gallinat, 2015; Smucny et al., 2022).

Working memory deficits are closely related to long-term prognosis and significantly impact patients' future recovery and social functioning; however, effective treatment options remain lacking. In recent years, researchers have proposed temporal interference stimulation (TIs) technology (Grossman et al., 2017), also known as noninvasive deep brain stimulation. Compared with traditional neuromodulation approaches, TIs demonstrates clear advantages in noninvasiveness, targeting and focality, and the capacity to induce specific frequency responses in neurons, providing a reliable theoretical basis for TIs to improve WMD in SCZ. Therefore, investigating the clinical effectiveness, brain region specificity, and underlying mechanisms of TIs intervention holds significant meaning for both clinical treatment and basic research.

First, confirming the therapeutic effectiveness of TIs for WMD in SCZ can provide new options for clinical treatment of SCZ and precise regulation of other mental disorders. Compared with other noninvasive neuromodulation techniques, TIs offers better spatial resolution, targeting, and noninvasiveness, while providing a more direct method to regulate neuronal responses at specific frequencies (Grossman et al., 2018). Consequently, TIs can achieve noninvasive targeting of specific brain regions without affecting other areas, avoiding potential risks associated with invasive deep brain stimulation surgery. Moreover, its unique modulation approach enables target brain regions to generate neural responses at desired oscillation frequencies. However, whether TIs' improvement effect on WMD in mental disorders is similar to or even superior to traditional transcranial alternating current stimulation (tACS) remains unknown. Therefore, verifying the clinical efficacy of TIs for WMD in SCZ demonstrates good innovation and advancement, with prominent clinical significance. Additionally, TIs can effectively circumvent the traditional trade-off between depth and focality, showing good potential clinical value when addressing the precise regulation needs for major mental disorders. Research on TIs effectiveness verification and mechanism exploration will not be limited to clinical applications in SCZ patients; this model will provide a good demonstration for developing non-pharmacological treatment approaches based on precise neuromodulation for other major brain diseases (depression, substance addiction, tic disorders in children, etc.) and for mechanism analysis.

Second, exploring target brain region specificity represents an important issue in the field of working memory neuromodulation, as both IPL and DLPFC are closely related to working memory performance. Investigating whether TIs shows specificity in regulatory effects between IPL and DLPFC and its underlying mechanisms holds important significance for understanding the functions of these two brain regions in working memory improvement in SCZ, and may provide new clues for target region selection in traditional neuromodulation approaches. In recent years, the regulatory effects of tACS on working memory have been influenced by multiple factors, with target brain region specificity being one of the most important. Previous studies have suggested that theta oscillation-based tACS targeting the frontal lobe (DLPFC) or parietal lobe (IPL) produces different working memory improvement effects (Grover et al., 2022;

Samantha J Booth et al., 2022), demonstrating the existence of brain region specificity in tACS intervention. Some researchers have also suggested that TIs' neural mechanisms may share certain similarities with tACS (Guo et al., 2023; Zhang et al., 2022). Therefore, whether TIs, as a highly targeted technology, still exhibits target brain region specificity when intervening in WMD in SCZ remains to be further verified. Thus, it is necessary to design experiments to explore the brain region specificity of TIs intervention, which is important for clarifying the roles and positions of IPL and DLPFC in working memory improvement in SCZ and can lay a foundation for working memory deficit regulation and neural mechanism exploration.

Third, the neural mechanisms underlying TIs regulation of behavior remain to be explored. Comparing changes at the brain mechanism level before and after TIs regulation can not only provide new evidence for neural mechanism analysis of TIs but also lay a foundation for exploring the neural mechanisms of WMD in SCZ. In recent years, some researchers have found that theta rhythm and theta-gamma cross-frequency coupling play key roles in WMD in SCZ patients (Adams et al., 2020; Barr et al., 2017; Lynn & Sponheim, 2016). Our pilot experiments and preliminary research have also suggested that theta oscillation-based TIs can effectively intervene in WMD in SCZ patients and rat models, demonstrating the importance of theta rhythm in the brain. Therefore, comparing changes in multi-brain region activity, cross-frequency coupling, and inter-regional coordination mechanisms before and after TIs regulation can further explore the multi-level regulatory mechanisms of TIs, examine the association between TIs regulatory mechanisms and the neural mechanisms of WMD in SCZ, provide new evidence for mechanism analysis of TIs, and offer further evidence for the important role of theta rhythm or cross-frequency coupling in working memory deficits.

In summary, confirming the therapeutic effectiveness and brain region specificity of theta oscillation-based TIs for WMD in SCZ and exploring its neural mechanisms can provide new options for clinical treatment of SCZ and precise regulation of other mental disorders, help clarify the similarities, differences, and respective roles of IPL and DLPFC in working memory improvement, and provide new evidence and theoretical support for mechanism analysis of TIs regulation and working memory mechanism exploration. Therefore, from the perspectives of theoretical construction and practical application, research exploring the clinical intervention and mechanism of action of theta oscillation-based TIs for WMD in SCZ is highly necessary.

2 Current Status and Trends of TIs Research

2.1 Basis for Effectiveness of TIs in Intervening WMD in SCZ Patients

2.1.1 Basic Principles of TIs In 2017, Grossman et al. proposed the concept of temporal interference stimulation technology that can noninvasively regulate deep brain nuclei (Grossman et al., 2017). The principle of this modulation method is that a single high-frequency electric field (>1000 Hz) cannot elicit neuronal responses. However, when two high-frequency electric fields are simultaneously applied with a small frequency difference (e.g., 2000 Hz and 2010 Hz), neurons in the interference (superposition) region of the two fields will be activated at this difference frequency (envelope frequency: 10 Hz) and begin firing at nearly the same frequency.

At the behavioral level of TIs: When researchers used TIs to modulate the motor cortex of mice, they could induce forelimb movement. When the envelope frequency was changed (from 1 Hz to 15 Hz), the forelimb movement frequency of the mice changed accordingly. Researchers verified this temporal interference stimulation concept through simple physical modeling and phantom experiments, and observed in vivo that TIs caused mouse neurons to fire at specific envelope frequencies (e.g., 10 Hz), while other irrelevant brain regions along the electric field path were not affected (Grossman et al., 2017).

At the physical mechanism level of TIs: Mirzakhalili et al.' s work exploring the biophysical principles of TIs showed that current rectification mediated by ion channels enables neurons to respond to TIs at specific frequencies (Mirzakhalili et al., 2020). Grossman et al. suggested that the inherent low-pass filtering characteristics of neuronal cell membranes lead to the TIs phenomenon (Grossman et al., 2017).

At the neural mechanism level of TIs: Previous research evidence indicates that the electric field strength and current intensity of TIs cannot directly cause neurons to generate action potentials. Instead, TIs regulates neuronal responses through subthreshold modulation via phase synchronization (Howell & McIntyre, 2021), which is quite similar to traditional tACS in biological mechanisms (Guo et al., 2023; Tavakoli & Yun, 2017). tACS has also been proven to improve working memory (Samantha J Booth et al., 2022). Additionally, some researchers have pointed out that TIs can elicit responses in pyramidal neurons (Cao & Grover, 2020), and recent studies suggest that pyramidal neurons are essential for working memory and participate in all phases of working memory (Vogel et al., 2022). Therefore, from these perspectives, we have reason to speculate that TIs can regulate working memory.

2.1.2 Safety and Focality of TIs Regarding safety: Rampersad et al. used finite element methods to simulate the electric field generated by TIs in the human brain, showing that TIs produces similar electric field intensity in deep brain regions as transcranial alternating current stimulation but with less stimulation to superficial regions (Rampersad et al., 2019). Experimenters conducted TIs experiments on awake mice and performed immunohistochemical detection using DNA damage markers and microglial markers 24 hours later. They found that TIs did not change neuronal density or apoptosis numbers, nor did it cause inactivation of microglia and astrocytes (Grossman et al., 2017). Most importantly, experiments on healthy human subjects by domestic and international researchers have shown that using conventional stimulation parameters (e.g., 2 mA, 20/70 Hz, 30 min) is safe (Piao et al., 2022), with minor and tolerable side effects similar to those caused by traditional tACS (Piao et al., 2022; Violante et al., 2022; Zhang et al., 2022). These studies all demonstrate the clinical safety of TIs.

Regarding focality: Some researchers have optimized electrode settings and stimulation parameters to achieve better focality and greater electric field intensity (Cao & Grover, 2020), ensuring the focality of TIs in practical applications. Compared with single-channel TIs, multi-channel TIs can significantly improve its focality (Song et al., 2021). Furthermore, some studies have attempted to use more advanced algorithmic methods (such as artificial neural networks) to design TIs stimulation parameters, achieving more focal stimulation in single individuals (Stoupis & Samaras, 2022). For example, one study found that specific artificial intelligence algorithms could design high-focality TIs technology to effectively and noninvasively restore vision (C. Wang et al., 2021). Additionally, researchers have used TIs to locate epileptogenic sites in epilepsy patients and can induce behavioral responses and electrophysiological changes similar to implanted electrodes, proving that TIs can achieve precise stimulation of local brain regions without many electrodes and can therefore be used to accurately locate epileptic foci (Collavini et al., 2021). Therefore, compared with traditional regulation methods, TIs demonstrates superior targeting and focality for target regions than tACS. While ensuring safety, future research can attempt focal regulation of deep brain regions.

2.1.3 Evidence of TIs Regulating Individual Behavior and Comparison with Traditional Methods like tACS Regarding motor function improvement: In 2022, Ma et al.' s study first demonstrated that 20/70 Hz TIs could enhance motor function in healthy subjects (Ma et al., 2021). Meanwhile, evidence from another research group showed that TIs, similar to transcranial direct current stimulation (tDCS), could increase functional connectivity between primary and secondary motor cortices (Zhu et al., 2022). Related research also indicates that TIs targeting the striatum at 80 Hz can modulate neuron activity in the striatum related to motor learning (Vassiliadis et al., 2024).

Regarding memory capacity modulation: Using healthy human subjects, Grossman' s research team showed that prolonged exposure to 5 Hz TIs targeting the hippocampus could improve memory accuracy, and used simulation and actual measurement to demonstrate the controllability and targeting of TIs in regulating hippocampal activity during memory tasks (Violante et al., 2023). Meanwhile, Zhang et al. also proved that TIs could modulate working memory performance in healthy human subjects under high task difficulty, with regulatory effects similar to tACS (Zhang et al., 2022).

In summary, previous research evidence shows that TIs can effectively regulate behavior in normal healthy subjects, with regulatory effects similar to traditional methods. It should be noted that the similarity between TIs and traditional methods in improvement effects shown in previous research may be due to ceiling effects in regulating normal subjects' behavior.

Compared with traditional methods like tACS, TIs offers better focality and higher spatial resolution, enabling precise regulation of target brain regions while achieving modulation of deep brain regions without affecting cortical regions. TIs avoids diffuse effects, is more controllable, and has stronger targeting.

Therefore, considering the aforementioned similarities in regulatory mechanisms between TIs and tACS, combined with the effectiveness of TIs in healthy subjects disclosed in existing research, we hypothesize that TIs can effectively intervene in working memory deficits in schizophrenia patients for clinical WMD intervention. Additionally, given TIs' superior precise regulation capability and targeting compared to tACS, and considering ceiling effects in normal subjects, we speculate that TIs may produce better improvement effects than tACS in SCZ patients.

Thus, clinically applying TIs to intervene in working memory deficits in SCZ for effectiveness verification and exploring its underlying neural mechanisms is important and urgent. TIs may be a very promising tool in future clinical treatment of SCZ and other neuropsychiatric disorders.

2.2 Two Key Brain Regions for WMD in SCZ (IPL and DLPFC)

2.2.1 Theta Rhythm' s Key Role in WMD in SCZ Patients Rhythmic neural electrical activity forms the basis of brain cognitive functions. Whether in single neuron firing, neuronal ensemble activity, or neural network activity, certain rhythmic patterns emerge, known as brain neural rhythms (Uhlhaas & Singer, 2010). A very important rhythm in the brain is theta rhythm, generally believed to depend on the interaction between the medial septal nucleus-hippocampal neural circuit or local interactions between interneurons and pyramidal cells in the hippocampal region (Herweg et al., 2020). Through connections between the prefrontal cortex and hippocampus or within neural networks, we can also observe prominent theta rhythm in the prefrontal cortex (Pignatelli et al., 2012). Research has found corresponding relationships between theta rhythm and many behaviors, with theta rhythm playing a key role in memory processes (Herweg et al., 2020). It is believed that during the information encoding phase, the peak phase of theta rhythm corresponds to long-term potentiation, while during the information retrieval phase, the trough phase corresponds to long-term depression, meaning theta rhythm regulates synaptic plasticity (Hasselmo & Stern, 2014).

For working memory, parietal theta rhythm plays important roles in both information storage and manipulation, specifically manifested by increased parietal theta rhythm amplitude during working memory maintenance as memory load and task demands increase (Palva & Palva, 2011; Sauseng et al., 2010). Additionally, a recent study suggests that DLPFC theta rhythm is closely related to the information maintenance phase of working memory (Brzezicka et al., 2019). Griesmayr et al. found that compared with simple memory tasks, DLPFC theta rhythm activity during working memory maintenance is more pronounced in high-difficulty tasks (Griesmayr et al., 2010).

Related research on schizophrenia patients suggests that amplitude abnormalities of theta rhythm in parietal and frontal regions and phase synchronization abnormalities of theta rhythm between brain regions have very strong connections with WMD in SCZ (Adams et al., 2020; Moran & Hong, 2011). Although conclusions from these studies are not entirely consistent, they all suggest important information: SCZ patients have reduced ability to adjust theta rhythm in the two key brain regions of IPL and DLPFC (Lynn & Sponheim, 2016).

2.2.2 Brain Region Specificity of Theta Oscillation tACS in Regulating Working Memory Behavior The mechanism of transcranial alternating current stimulation involves regulating brain activity by inducing neural oscillations and long-term synaptic plasticity, thereby modulating cognitive processes (Elyamany et al., 2021). Rhythmic tACS can induce neural oscillation activity in the same frequency band in the stimulated brain region. Using normal elderly populations as subjects, Grover et al. demonstrated obvious brain region specificity when using theta oscillation tACS to improve working memory in older adults. Theta oscillation tACS targeting the IPL could effectively improve working memory in older adults, while theta oscillation tACS targeting the DLPFC did not cause significant working memory improvement (Grover et al., 2022). Jaušovec et al. also provided similar evidence: when using theta oscillation tACS to stimulate the left parietal lobe and left frontal lobe separately during working memory span tests, they found that compared with sham stimulation, subjects' working memory storage capacity improvement was most obvious when stimulating the left parietal lobe, while no such effect was found when stimulating the frontal lobe (Jaušovec & Jaušovec, 2014; Jaušovec et al., 2014). However, Alekseichuk et al. found that theta oscillation tACS targeting the frontal lobe could also regulate working memory behavior (Alekseichuk et al., 2016). Although there are inconsistencies in conclusions among these studies, Booth et al.' s systematic review shows that theta oscillation tACS conducted in the posterior brain region can effectively regulate working memory with strong evidence, while theta oscillation tACS in the anterior brain region is less effective and weaker than in the posterior region (Booth et al., 2022).

In other words, these studies indicate that theta oscillation tACS exhibits brain region specificity when regulating working memory, with posterior brain region regulation effects being superior to anterior brain region effects. Combined with the aforementioned similarities between TIs and tACS at neural mechanism and behavioral levels, we hypothesize that theta oscillation TIs may exhibit brain region specificity when targeting IPL and DLPFC brain regions to intervene in WMD in SCZ patients.

However, one point requiring our attention: research on tACS as a potential tool for treating WMD in SCZ is still in its infancy, and its research results have varying degrees of controversy. Hoy et al. found that 40 Hz tACS regulation on the left DLPFC did not change working memory behavior in SCZ patients (Hoy et al., 2016). Another research group found that simultaneous theta oscillation tACS regulation of the left DLPFC and left posterior parietal region could improve working memory task performance, and the improvement caused by five consecutive days of tACS stimulation could still be observed in a 50-day follow-up (Sreeraj et al., 2017; Sreeraj et al., 2019). However, no one has used theta oscillation tACS targeting the IPL brain region to improve WMD in SCZ patients, and its regulatory effect still requires further verification.

In summary, although IPL and DLPFC are two core key brain regions for working memory impairment in SCZ patients, and previous studies have suggested that SCZ patients' working memory impairment is closely related to reduced theta rhythm adjustment ability in IPL and DLPFC brain regions, theta oscillation-based tACS exhibits brain region specificity when regulating working memory (posterior brain regions are superior to anterior brain regions). Combined with the aforementioned similarities between TIs and tACS, we speculate that theta oscillation TIs may exhibit brain region specificity when targeting IPL and DLPFC brain regions to regulate WMD in SCZ patients.

2.3 Possible Neural Mechanisms of TIs Regulating WMD in SCZ Patients

Based on different frequency information, neural rhythms in the brain can be divided into Delta (<4 Hz), Theta (4~7 Hz), Alpha (8~13 Hz), Beta (14~30 Hz), and Gamma (>30 Hz) rhythms (Figure 2 [Figure 2: see original paper]A, though different studies have slight variations in classification). In addition to spontaneously generated neural rhythms, we can also change rhythmic activity in corresponding frequency bands in the brain through external rhythmic stimulation (tACS/TMS, etc.), triggering phase locking (Adaikkan & Tsai, 2020), a phenomenon known as "neural entrainment." The phenomenon where theta oscillation-based neural entrainment leads to changes in brain theta rhythm, thereby altering higher brain functions such as learning and working memory, has received considerable attention in current research, and theta oscillation TIs may be one of the methods to induce neural entrainment phenomena. However, the possible neural mechanisms behind theta oscillation TIs intervention for WMD in SCZ patients remain to be further explored.

Previous EEG and MEG research evidence suggests that the neural mechanisms behind theta oscillation tACS regulation of working memory mainly manifest in the following aspects:

Theta rhythm amplitude and power: When Vosskuhl et al. used tACS below individual theta frequency to regulate subjects' working memory, they found that theta rhythm power in parietal brain regions significantly increased (Vosskuhl et al., 2015). However, Chander et al.' s study showed that tACS stimulation reduced theta rhythm power in frontal midline regions (Chander et al., 2016). Pahor et al. found that theta oscillation tACS in bilateral parietal and right frontoparietal regions could reduce resting-state theta rhythm amplitude

(Pahor & Jaušovec, 2017). Although changes caused by theta oscillation tACS remain controversial, theta rhythm amplitude and power are potential indicators we need to focus on when exploring TIs regulation mechanisms.

Theta rhythm phase synchronization: Theta rhythm phase-phase coupling can effectively promote cross-brain-region information exchange. Alekseichuk et al. found that theta oscillation tACS caused enhanced global theta phase synchronization in brain networks (Alekseichuk et al., 2016), and this enhancement was positively correlated with working memory behavior. Reinhart et al.' s 2019 study showed that high-precision theta oscillation tACS led to enhanced phase synchronization between frontal and temporal brain regions (Reinhart & Nguyen, 2019). These studies suggest that theta oscillation tACS may cause enhanced inter-brain-region phase synchronization, which may be a possible EEG-level change for TIs regulation of working memory behavior.

2.3.1 Cross-Frequency Coupling Mechanism of Theta Oscillation tACS in Regulating Behavior In addition to theta rhythm, brain gamma rhythm is also considered to be closely related to individual behavior. For example, research results suggest that square pulse envelope modulation based on gamma oscillation can affect sleep behavior in mice (Liu et al., 2021). For working memory, neural oscillations in different frequency ranges can, in principle, work and operate independently, but experiments have found that they may appear simultaneously and subsequently modulate and interact with each other. This dynamic coupling relationship between neural oscillations in different frequency bands is called cross-frequency coupling (CFC). More and more studies have found that CFC plays a very key role in working memory (Abubaker et al., 2021). CFC usually includes phase-amplitude coupling (PAC), phase-phase coupling, and amplitude-amplitude coupling.

Phase-amplitude coupling: In working memory tasks, PAC is a crucial coupling relationship. PAC refers to the phenomenon where the phase of a low-frequency oscillation and the amplitude of a high-frequency oscillation have phase synchronization. PAC within brain regions reflects the information processing and integration capability of that brain region. Among these, theta-gamma rhythm PAC is very relevant to working memory (Senkowski & Gallinat, 2015). By synchronously superimposing gamma oscillations between the peaks or troughs of theta oscillations, multiple objects in working memory can be maintained simultaneously. Researchers believe that the number of gamma oscillations coupled in a single theta oscillation cycle represents the number of working memory items. The longer the theta oscillation cycle and the slower the frequency, the more gamma oscillations can be coupled, and the larger the working memory capacity (Lisman, 2010; Lisman & Buzsáki, 2008; Lisman & Jensen, 2013).

Vosskuhl et al. increased subjects' working memory capacity by using tACS to reduce individual theta rhythm frequency, thereby increasing the number of coupled gamma oscillations (Vosskuhl et al., 2015). Wolinski et al. further confirmed this theory, finding that 4 Hz oscillation tACS could increase working memory capacity, while 7 Hz oscillation tACS would decrease working memory capacity (Wolinski et al., 2018). Bender et al. also provided related evidence that 4 Hz oscillation tACS could improve individual working memory performance under high task difficulty (Bender et al., 2019). In 2022, Grover et al. used 4 Hz oscillation tACS targeting the IPL brain region in older adults and found significant improvement in working memory behavior (Grover et al., 2022). This evidence points to an important conclusion: 4 Hz oscillation tACS targeting the IPL brain region helps improve working memory behavior through cross-frequency coupling, highlighting the importance of cross-frequency coupling in WMD.

Meanwhile, from the perspective of working memory neural mechanisms: In recent years, more and more researchers believe that PAC, especially theta-gamma rhythm PAC abnormalities, is a very important cause of working memory deficits in SCZ, elderly populations, and other groups (Abubaker et al., 2021; Barr et al., 2017; Lynn & Sponheim, 2016; Reinhart & Nguyen, 2019; Senkowski & Gallinat, 2015). Combined with the aforementioned similarity between TIs and tACS in regulatory mechanisms, we hypothesize that providing 4 Hz theta oscillation TIs stimulation may restore PAC abnormalities in SCZ patients' brain regions, and PAC changes as a neural mechanism may significantly improve WMD in SCZ patients. However, this hypothesis requires experimental verification.

To verify the explanatory power of the cross-frequency coupling theoretical model, and given that a large amount of previous research evidence suggests that low-frequency theta oscillation (4 Hz) helps improve working memory in SCZ patients, this study selected 4 Hz as the frequency for theta oscillation TIs to improve WMD in SCZ patients.

In summary, theta rhythm abnormalities and theta-gamma rhythm cross-frequency coupling mechanisms play very important roles in working memory behavior. However, whether TIs can significantly improve WMD in SCZ patients through the above neural mechanisms remains unclear, and whether behavioral changes can be supported by the aforementioned neural mechanisms still requires experimental evidence and demonstration.

3 Research Design

When using theta oscillation TIs to improve WMD in SCZ patients, the following three aspects warrant investigation:

First, as a cutting-edge international neuromodulation technology, TIs offers significant advantages in noninvasiveness, targeting and focality, and the capacity to induce specific responses in neuronal ensembles, circumventing the shortcomings of traditional regulation methods. However, its intervention effectiveness for WMD in SCZ patients remains to be verified, and whether its improvement effects significantly differ from traditional tACS efficacy remains unclear.

Second, whether theta oscillation-based TIs exhibits brain region specificity when targeting IPL and DLPFC brain regions to improve WMD in SCZ patients is uncertain. Whether theta oscillation TIs produces stronger improvement effects when targeting the DLPFC brain region or the IPL brain region remains to be further explored.

Third, the neural mechanisms through which theta oscillation TIs regulates WMD in SCZ patients remain unclear. Whether TIs regulation causes changes in theta rhythm energy within brain regions, changes in theta rhythm phase synchronization between brain regions, or changes in theta-gamma rhythm cross-frequency coupling strength remains to be further explored. Mechanism analysis of TIs regulation and WMD mechanisms requires evidence support.

Fourth, considering the influence of heterogeneity and other factors in SCZ patients, this project will also conduct self-control from the perspective of crossover trials of clinical intervention methods to further confirm and compare the clinical efficacy of TIs and tACS.

Research on the intervention effectiveness of TIs for clinical symptoms of mental disorders has important significance and application value for clinical treatment. Therefore, it is very necessary to conduct appropriate experimental research to carry out efficacy verification of TIs for WMD in SCZ, explore whether its efficacy exhibits brain region specificity, and further reveal the neural mechanisms of TIs in treating WMD.

Therefore, based on previous research, this study uses theta oscillation (4 Hz) TIs and theta oscillation (4 Hz) tACS to target the IPL brain region in the parietal cortex, combined with sham stimulation groups, to confirm the clinical efficacy of TIs in intervening WMD in SCZ patients and compare it with traditional methods. Second, this study will also use theta oscillation (4 Hz) TIs to target the DLPFC brain region (BA9) in the frontal cortex to reveal whether TIs exhibits brain region specificity in improving WMD in SCZ patients. Finally, EEG monitoring will be used to examine changes in working memory behavior-based EEG in patients before and after TIs regulation to explore the neural mechanisms of TIs improvement of working memory and the potential mechanisms of WMD in SCZ. Additionally, given the large individual differences in brain structure among SCZ patients, this project will adopt individual modeling during implementation.

In summary, this project will be carried out from both behavioral and neural mechanism levels, specifically divided into the following four studies:

3.1 Study 1: Intervention Effectiveness of Theta Oscillation TIs for WMD in SCZ Patients and Efficacy Comparison

Using a randomized controlled study, the classic behavioral paradigm most commonly used in visual working memory—the Delayed Matching to Sample (DMS) task—will serve as the assessment tool for working memory behavior and cognitive function in SCZ patients. Simultaneously, EEG recordings and clinical scale assessments will be combined to collect multi-dimensional data. One hundred first-episode schizophrenia patients aged 18-55 will be enrolled as research subjects and randomly and evenly assigned to different experimental groups. The study will set up four groups: TIs group (4 Hz), tACS stimulation group (4 Hz), TIs sham stimulation group, and tACS sham stimulation group, all targeting the IPL brain region (Brodmann area 40, BA40). The project will evaluate the efficacy of theta oscillation TIs on WMD in SCZ patients through multi-dimensional cross-validation using cognitive function battery assessments and DMS behavioral changes, then compare behavioral changes with the theta oscillation tACS group to verify whether there are significant differences in improvement efficacy between theta oscillation TIs and theta oscillation tACS. Compared with healthy populations, SCZ patients have different lesion locations, disease severity, or clinical characteristics, with large individual differences in brain models, which may significantly affect TIs' targeting, focality, and current attenuation. Therefore, during TIs intervention implementation, this project will use SimNIBS software to import individualized imaging data from MRI scans of each SCZ patient to complete individualized modeling. After personalized modeling is completed, this project will combine preliminary stimulation parameters provided by HD-target software and through code writing in SimNIBS software, continuously iterate and update to achieve optimal configuration of personalized electrode positions, current intensity, and other stimulation parameters. When designing the DMS task, we designed working memory tasks with different difficulty levels to examine whether the efficacy of theta oscillation TIs and tACS applies to all task difficulty conditions, providing clues for mechanism analysis and making it more targeted. Additionally, setting different task difficulty levels can avoid interference from potential "ceiling effects" in behavioral studies on treatment effects.

3.2 Study 2: Brain Region Specificity of TIs in Improving WMD in SCZ Patients

Based on Study 1, Study 2 will still use a randomized controlled study, employing the DMS task combined with EEG recordings and clinical scale assessments to collect multi-dimensional data. Fifty first-episode SCZ patients will be enrolled as research subjects and randomly and evenly assigned to the TIs group (4 Hz) and TIs sham stimulation group, but Study 2 will target the DLPFC (BA9) brain region. Therefore, Study 2 will combine the clinical efficacy of TIs targeting the IPL brain region from Study 1 to verify whether brain region specificity exists when TIs improves WMD in SCZ patients.

3.3 Study 3: Neural Mechanisms of TIs in Improving WMD in SCZ Patients

Study 3 will use EEG data collected in Studies 1 and 2 to conduct comparative analysis of changes in multiple indicators before and after TIs regulation, including theta oscillation energy in brain regions, inter-brain-region theta rhythm phase synchronization, and theta-gamma cross-frequency coupling. Simultaneously, it will compare whether there are significant differences in changes of the aforementioned indicators between groups, examine the correspondence between EEG data changes and behavioral-level changes, to parse the neural mechanisms of TIs regulation of working memory behavior in SCZ patients and explore whether EEG-level changes can effectively support behavioral-level changes.

3.4 Study 4: Crossover Trial of TIs and tACS in Improving WMD in SCZ Patients

To effectively avoid the impact of heterogeneity factors in SCZ patients, Study 4 will newly enroll 50 first-episode SCZ patients as research subjects, evenly assigned to 2 groups. One group of patients will first receive TIs intervention treatment, followed by tACS intervention treatment. We will conduct self-comparison at three key time points—baseline, end of TIs treatment, and end of tACS treatment—using cognitive function battery assessments and DMS behavioral changes to evaluate the efficacy of TIs and tACS on WMD in SCZ patients. Meanwhile, the other group of patients will first receive tACS intervention treatment, followed by TIs treatment, with corresponding assessments at the same three time points to balance the impact of intervention order on trial results.

4 Innovation Points

4.1 Innovation in TIs as a Neuromodulation Intervention Method

Currently, in the treatment of cognitive dysfunction and even WMD in SCZ clinical patients, drug therapy has limited overall efficacy, with a lack of effective drugs for treating WMD in SCZ patients. In terms of physical regulation, the intervention effects of various techniques are not ideal: tDCS has inconsistent regulatory effects due to diffuse target sites; the clinical efficacy and mechanisms of tACS intervention still require exploration, and its clinical application faces challenges due to insufficient spatial resolution and inability to target deep brain regions; TMS has weak effects, high requirements for operators, and risks of inducing epilepsy, requiring further optimization. As a current international frontier and popular emerging neuromodulation technology, TIs possesses multiple advantages including noninvasiveness, targeting and focality, and effectiveness in inducing specific frequency responses in neurons. Moreover, our preliminary clinical pilot experiments and animal experiments on this technology' s efficacy verification provide strong evidence support. Therefore, this project uses TIs technology to intervene in WMD in SCZ clinical patients and compares it with traditional tACS efficacy, with definite treatment effects and optimistic prospects. Using the latest TIs technology to intervene in WMD in SCZ and conduct efficacy verification is a feature of this study. Currently, there are no studies using TIs alone for clinical intervention of WMD in SCZ and comparing its efficacy with traditional methods, making this project highly innovative and advanced. Simultaneously, this study will also verify the efficacy of theta oscillation tACS in intervening WMD in SCZ, with only two previous case studies on this aspect.

4.2 Research on Brain Region Specificity and Mechanism Analysis Based on Cross-Frequency Coupling

Brain region specificity: In recent years, the frontal cortex and parietal cortex, theta oscillation and gamma oscillation represent an international frontier research hotspot on whether neuromodulation methods exhibit frequency and location specificity in improving working memory behavior, especially whether low-frequency theta oscillation in the parietal cortex can effectively improve working memory behavior. Clarifying this research question is very important for working memory intervention research. However, there is currently a lack of evidence for brain region specificity when TIs regulates WMD in SCZ. Therefore, by using TIs as a neuromodulation method to intervene in neural oscillation rhythms in different brain regions, we can establish causal relationships between brain region—theta rhythm—working memory behavior. On one hand, this helps clarify the degree and role of IPL and DLPFC brain regions in working memory processing; on the other hand, it can provide evidence support for future directions of TIs technology intervention for WMD, with prominent significance and innovation for clinical physical therapy of SCZ.

Cross-frequency coupling theory: This project uses specific low-frequency (4 Hz) theta oscillation TIs technology to improve WMD, combined with working memory behavioral paradigms, to parse neural mechanisms from multiple analysis indicator perspectives (brain region rhythms and cross-frequency coupling, as well as inter-brain-region phase synchronization). This helps verify the relationship between cross-frequency coupling mechanism abnormalities (the higher the theta oscillation frequency, the fewer gamma oscillations coupled within a single cycle, and the smaller the working memory capacity) and WMD, providing correlational evidence for theoretical construction of working memory regarding cross-frequency coupling, and providing theoretical references for mechanism analysis of other neuromodulation methods, representing a relatively important innovation point.

The user wants me to translate a specific section of a Chinese academic paper. The section is "### 4.3 Innovation in Clinical and Basic Research Application Prospects" .

Let me analyze the requirements: 1. Translate ONLY this section 2. Keep the same structure (### heading) 3. Remove ALL Chinese characters - not even one 4. Handle proper nouns correctly (pinyin for names, English for journals/institutions if known) 5. Use standard English technical terms 6. Maintain academic tone 7. Preserve any LaTeX/math if present (though I don' t see any in this section) 8. Return ONLY the translated section, nothing else

Let me go through the text carefully:

Original Chinese text:

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### 4.3 Innovation in Clinical and Basic Research Application Prospects

**Clinical application expansion:** Starting with schizophrenia, after verifying the effica

**Basic research:** On one hand, research on TIs technology effectiveness verification and m

**Expansion to deep brain region targeting:** It should be noted that for superficial brain

In summary, using TIs technology to verify effectiveness in intervening WMD, exploring brai
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Key terms to translate: - 思路 -> approach/methodology (but the user says "思路" appears, I need to translate it) - TIs technology -> TIs technology (keep as is, it' s an acronym) - tACS -> tACS (keep as is) - TMS -> TMS (keep as is) - WMD -> WMD (working memory deficit, keep acronym) - SCZ -> SCZ (schizophrenia, keep acronym) - IPL -> IPL (inferior parietal lobule, keep acronym) - DLPFC -> DLPFC (dorsolateral prefrontal cortex, keep acronym)

Wait, I see the user mentioned "Chinese characters found: 路, 思" but in the text provided, I see "思路" which means "thought/approach". The user says these appear to be mixed technical content and proper nouns. I think they want me to translate "思路" appropriately, not treat it as a proper noun.

Let me translate section by section:

Section 1: Clinical application expansion "Starting with schizophrenia, after verifying the efficacy of TIs technology for schizophrenia, the overall research scheme and 思路 of this project can be extended to other major brain diseases, such as depression, substance addiction, tic disorders in children, etc." -> "Starting with schizophrenia, after verifying the efficacy of TIs technology for this condition, the overall research scheme and approach of this project can be extended to other major brain diseases, such as depression, substance addiction, tic disorders in children, etc."

"This model provides a good demonstration for developing noninvasive deep brain stimulation-based approaches for other major diseases, provides basis for establishing early identification indicator systems for diseases, and offers solutions for feedback regulation and personalized diagnosis and treatment of these diseases." -> "This model provides a good demonstration for developing noninvasive deep brain stimulation-based approaches for other major diseases, establishes a basis for early identification indicator systems, and offers solutions for feedback regulation and personalized diagnosis and treatment."

Section 2: Basic research "On one hand, research on TIs technology effectiveness verification and mechanism exploration can provide clinical verification evidence for TIs technology-induced neuronal activation." -> "On the one hand, research verifying the effectiveness of TIs technology and exploring its mechanisms can provide clinical evidence for TIs-induced neuronal activation."

"On the other hand, beyond conventional methods such as tACS and TMS, it provides a new neuromodulation method, offering relatively direct causal arguments and effective means for basic research on attention, learning behavior, emotion improvement, and other aspects of intervention regulation and mechanism analysis." -> "On the other hand, beyond conventional methods such as tACS and TMS, it provides a novel neuromodulation approach, offering relatively direct causal evidence and effective tools for basic research on intervention regulation and mechanism analysis in attention, learning behavior, emotion improvement, and other domains."

Section 3: Expansion to deep brain region targeting "It should be noted that for superficial brain regions such as the frontal and parietal lobes, compared with tACS, TIs technology' s advantages in focality and targeting are relatively weaker, its electric field simulation calculation is more difficult, and the envelope wave position/intensity formed by difference-frequency electric fields shows greater individual variability." -> "It should be noted that for superficial brain regions such as the frontal and parietal lobes, TIs technology' s advantages in focality and targeting are relatively weaker compared with tACS, its electric field simulation is more complex, and the position/intensity of envelope waves formed by difference-frequency electric fields shows greater individual variability."

"Meanwhile, from the perspective of phase-coordinated stimulation and multi-brain-region synchronous stimulation, traditional tACS has already achieved high-precision regulation targeting phase, frequency, and multi-brain-region synchronization in working memory regulation, which TIs cannot achieve." -> "Meanwhile, from the perspective of phase-coordinated stimulation and multi-brain-region synchronous stimulation, traditional tACS has already achieved high-precision regulation targeting phase, frequency, and multi-brain-region synchronization in working memory regulation—capabilities that TIs cannot achieve."

"However, when conducting clinical intervention targeting deep brain regions (such as the hippocampus, basal ganglia, and related brain regions), TIs, as a noninvasive brain stimulation technique, indeed has strong and distinctive regulatory advantages." -> "However, when conducting clinical interventions targeting deep brain regions (such as the hippocampus, basal ganglia, and related brain regions), TIs, as a noninvasive brain stimulation technique, indeed possesses strong and distinctive regulatory advantages."

"Therefore, this project aims to preliminarily verify that TIs technology is effective when targeting superficial brain regions to treat WMD in SCZ patients, compare its clinical efficacy with traditional tACS methods, and provide feasibility for a new therapeutic approach." -> "Therefore, this project aims to preliminarily verify the efficacy of TIs technology when targeting superficial brain regions to treat WMD in SCZ patients, compare its clinical efficacy with traditional tACS methods, and establish feasibility for a novel therapeutic approach."

"This also provides reference for future research that may expand targeted brain regions to deep brain regions (such as the hippocampus, anterior cingulate cortex) to potentially enhance clinical efficacy." -> "This also provides a reference for future research that may expand targeted brain regions to deep brain regions (such as the hippocampus, anterior cingulate cortex) to potentially enhance clinical efficacy."

"While ensuring safety, improving its precision and focality can help enhance neuromodulation efficiency, with the expectation of approaching or even achieving the effects of invasive deep brain stimulation using noninvasive means." -> "While ensuring safety, improving its precision and focality can help enhance neuromodulation efficiency, with the expectation of approaching or even achieving the effects of invasive deep brain stimulation through noninvasive means."

Section 4: In summary "In summary, using TIs technology to verify effectiveness in intervening WMD, exploring brain region specificity, and parsing mechanisms provides a mechanism-based, promising new targeted noninvasive treatment method and theoretical support for SCZ, laying a clinical foundation for TIs application." -> "In summary, using TIs technology to verify its effectiveness in intervening WMD, exploring brain region specificity, and parsing mechanisms provides a mechanism-based, promising new targeted noninvasive treatment method and theoretical support for SCZ, laying a clinical foundation for TIs application."

"It helps clarify the roles of IPL and DLPFC brain regions and cross-frequency coupling theory in working memory improvement in SCZ, can be extended to treatment of other major brain diseases with definite and optimistic prospects, and provides new regulation methods and target brain region references for basic research." -> "It helps clarify the roles of the IPL and DLPFC brain regions and cross-frequency coupling theory in working memory improvement in SCZ, can be extended to the treatment of other major brain diseases with definite and optimistic prospects, and provides new regulation methods and target brain region references for basic research."

"Starting from this point, this project is expected to provide new solutions for clinical treatment of major brain diseases such as SCZ, with potential therapeutic application value, while providing new tools, new evidence, and new perspectives for brain mechanism exploration in basic research." -> "Starting from this foundation, this project is expected to provide new solutions for## References

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