**Underlying Mechanisms of Non-Invasive Brain Stimulation on the Cognitive and Mood Symptoms of Menopause: A Randomised, Sham-Controlled, Double-Blinded, Pilot Clinical Trial**

**Draft Clinical Trial Protocol**

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Table of Contents

[List of Abbreviations 4](#_Toc172288843)

[List of Figures and Tables 6](#_Toc172288844)

[1. Protocol Summary 7](#_Toc172288845)

[1.1 Project Synopsis 7](#_Toc172288846)

[1.2 Schedule of Activities 9](#_Toc172288847)

[2. Introduction 11](#_Toc172288848)

[2.2 Study Rationale 11](#_Toc172288849)

[2.3 Menopause 11](#_Toc172288850)

[2.4 Endocrinological Changes in the Menopause Transition 12](#_Toc172288851)

[2.5 Menopause Symptoms and Mechanisms 12](#_Toc172288852)

[Cognitive Symptoms 13](#_Toc172288853)

[Proposed Mechanisms for Cognitive Symptoms 13](#_Toc172288854)

[Psychological Symptoms 15](#_Toc172288855)

[Proposed Mechanisms for Psychological Symptoms 15](#_Toc172288856)

[2.6 Managing Menopause Symptoms 16](#_Toc172288857)

[2.7 Transcranial Magnetic Stimulation (TMS) 17](#_Toc172288858)

[Repetitive TMS (rTMS) 18](#_Toc172288859)

[Clinical Utility of rTMS for Improving Cognition 18](#_Toc172288860)

[rTMS Mechanisms for Improving Cognition 19](#_Toc172288861)

[Clinical Utility of rTMS for Improving Mood 20](#_Toc172288862)

[rTMS Impacts on Immunological Function 20](#_Toc172288863)

[rTMS Impacts on Autonomic Function 20](#_Toc172288864)

[Interactions Between rTMS and Sex Hormones 20](#_Toc172288865)

[Theta-Burst Stimulation (iTBS) 21](#_Toc172288866)

[2.8 Study Aims and Objectives 23](#_Toc172288867)

[3. Methodology 23](#_Toc172288868)

[1.1 Study Design and Intervention 23](#_Toc172288869)

[1.2 Study Population 24](#_Toc172288870)

[1.3 Inclusion and Exclusion Criteria 24](#_Toc172288871)

[1.4 Sample Size Determination 26](#_Toc172288872)

[1.5 Recruitment Strategy 26](#_Toc172288873)

[1.6 Randomisation and Blinding 27](#_Toc172288874)

[1.7 Ethical Considerations and Informed Consent 27](#_Toc172288875)

[1.8 Study Flow and Testing 28](#_Toc172288876)

[4. Primary Estimands (Neurocognition) 30](#_Toc172288877)

[5. Co-Primary Outcomes (Neurocognitive Mechanisms) 30](#_Toc172288878)

[6. Secondary Outcomes (Autonomic/Biochemical Mechanisms) 31](#_Toc172288879)

[7. Tertiary Outcomes (Cognition/Mood Effects) 32](#_Toc172288880)

[8. Potential Risks 33](#_Toc172288881)

[9. Adverse Event Reporting 34](#_Toc172288882)

[10. Statistical Considerations 35](#_Toc172288883)

[11. Project Significance 35](#_Toc172288884)

[12. References 37](#_Toc172288885)

# List of Abbreviations

|  |  |
| --- | --- |
| **AD** | Alzheimer’s disease |
| **AE** | Adverse event |
| **ADRs** | Adverse drug reactions |
| **AMS** | Australian Menopause Society |
| **APOE-e4** | Apolipoprotein epsilon 4 |
| **AR** | Adverse reaction |
| **ATP** | Adenosine Triphosphate |
| **Aβ** | Amyloid β |
| **BDNF** | Brain derived neurotrophic factor |
| **CNS** | Central nervous system |
| **Conners CPT 3** | Conners Continuous Performance Test 3 |
| **COX** | Cytochrome C oxidase |
| **CRP** | C Reactive Protein |
| **D-KEFS** | D-KEFS Verbal Fluency (Letter Fluency and Category Fluency) |
| **DHEA** | Dehydroepiandrosterone |
| **DLPFC** | Dorsolateral prefrontal cortex |
| **EEG** | Electroencephalograph |
| **ELISA** | Enzyme Linked Immunosorbent Assay |
| **EOG** | Electrooculogram |
| **FDA** | Food and Drug Administration |
| **FSH** | Follicle Stimulating Hormone |
| **GABA** | Gamma amino butyric acid |
| **GAD-7** | General Anxiety Disorder-7 |
| **GMV** | Grey matter volume |
| **HPO** | Hypothalamus-pituitary-ovarian |
| **HREC** | Human Research Ethics Committee |
| **HRV** | Heart rate variability |
| **IL-2** | Interleukin-2 |
| **LH** | Luteinising Hormone |
| **LTP** | Long term potentiation |
| **MACCS** | Memory and Cognitive Confidence Scale |
| **MDD** | Major Depressive Disorder |
| **MENQOL** | Menopause-Specific Quality of Life |
| **MHT** | Menopausal hormone therapy |
| **MMSE** | Mini Mental State Examination |
| **NAD** | Nicotinamide adenine dinucleotide |
| **NADH** | Nicotinamide adenine dinucleotide hydrogen |
| **PASAT** | Paced Auditory Serial Addition Test |
| **PHQ-9** | Patient Health Questionnaire-9 |
| **PISCF** | Participant Information Sheet and Consent Form |
| **PSQI** | Pittsburgh Sleep Quality Index |
| **RAAA** | Revised Artefact Aligned Average |
| **RAVLT** | Rey Auditory Verbal Learning Test |
| **RCT** | Randomised controlled trial |
| **rMT** | Resting motor threshold |
| **rTMS** | Repetitive transcranial magnetic stimulation |
| **SAE** | Serious adverse event |
| **SCC** | Subjective cognitive complaints |
| **SDMT** | Symbol Digit Modality Test |
| **STRAW +10** | Stages of Reproductive Aging Workshop +10 |
| **SUSAR** | Suspected unexpected serious adverse reaction |
| **TMS** | Transcranial magnetic stimulation |
| **TNF-alpha** | Tumour Necrosis Factor Alpha |
| **TRD** | Treatment-resistant depression |
| **VAS-F** | Visual Analogue Scale to Evaluate Fatigue Severity |
| **WSU** | Western Sydney University |

# List of Figures and Tables

**Table 1.** Schedule of Activities

**Table 2.** Summary of key meta-analyses assessing the use of iTBS on cognition and mood in healthy and clinical populations.

**Table 3.** Summary of key meta-analyses assessing the use of iTBS on cognition and mood in healthy and clinical populations.

**Figure 1.** Study flow diagram. Participants will receive either active or sham rTMS treatment. Follow up will occur at the precise four-week post-intervention mark. There will be three testing sessions in total: Baseline (Day 1), Endpoint (Day 5), and Follow Up (Week 5).

# Protocol Summary

## Project Synopsis

Menopause is defined as the permanent end of the menstrual cycle [1]. The cognitive and psychological symptom profiles associated with menopause are well-defined. Up to 67 % of females in the menopause transition report subjective cognitive complaints (SCCs) [2], and objective cognitive decline has also been noted in areas including verbal learning and memory, working memory and other executive functions [3]. Psychological complaints are common in the menopause transition, with 47 % of females living with menopause reporting depressed mood, and 37 % reporting high levels of anxiety [4]. The cognitive and mood symptoms associated with the menopause transition are often considered secondary to vasomotor symptoms, despite their profound impacts on activities of daily living and quality of life.

An emerging field of research is focused on exploring changes in brain bioenergetics across the menopause transition. The bioenergetic hypothesis for menopause is characterised by changes in white matter structure, energy utilisation and metabolism, and connectivity in regions involved in higher-order cognitive functions [5]. This hypothesis suggests that the menopause transition is a dynamic neuroendocrinological transition that may explain the cognitive and mood symptoms of menopause and emphasises the need for research into novel treatment options to address underlying mechanistic factors. Despite this, it is widely considered that the neurological changes seen in menopause may explain the increased risk of multifactorial hypometabolic conditions in females – such as dementia [6]. Most treatment options for managing menopause symptoms focus on vasomotor symptoms through menopausal hormone therapy (MHT). The lack of treatments available for managing the cognitive and psychological symptoms of menopause, coupled with the elevated risk of hypometabolic conditions and concerns about MHT, warrants the need for research into novel treatment options.

Intermittent theta burst stimulation (iTBS) is a neuromodulation technique that can alter cortical excitability, as a form of repetitive transcranial magnetic stimulation (rTMS). Repetitive TMS (rTMS) refers to applying repeated TMS pulses to specific brain regions [7], and has been found to be a promising non-invasive treatment for deficits in executive functioning in healthy adults and adults with cognitive impairments and treatment-resistant depression. Despite ample data demonstrating that iTBS has wide clinical utility, no such study has been conducted to explore the therapeutic potential of iTBS in managing cognitive and mood symptoms throughout the menopause transition.

The aim of this clinical trial is to assess the underlying mechanisms of iTBS in females in the late menopause transition, and to assess the relationship with cognition and mood. To accomplish this, the research will involve a randomised, sham-controlled, double-blinded pilot clinical trial comprising four empirical studies. Specific objectives of the clinical trial include characterising the potential neurocognitive (Objective 1; Study 1), autonomic (Objective 2; Study 2) and biochemical (Objective 3; Study 3) mechanisms of iTBS. Additionally, the clinical trial will explore a possible signal of efficacy via effect-size estimates of changes in cognitive and mood outcomes (Objective 4; Study 4).

Given the prevailing concerns around the lack of treatments for the cognitive and psychological symptom profiles associated with menopause, coupled with a lack of understanding of the underlying mechanisms, effective alternatives that can support females in the late menopause transition are urgently needed. iTBS may be a safe and effective therapeutic option to rescue the cognitive deficits and improve the psychological symptoms associated with the menopause transition. Findings from this clinical trial have the potential to advance our understanding of the underlying mechanisms that affect cognition and mood in menopause and offer the potential for new non-invasive treatments to mitigate symptoms. Downstream outcomes and innovations from this research may improve the experience of the 80,000 Australian women who move into the menopause transition each year and mitigate the financial impacts of untreated menopause symptoms on the workforce.

## Schedule of Activities

**Table 1.** Schedule of Activities

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Item | StudyOutcome | Online Screening | PhoneScreening | Baseline(Day 1) | Endpoint(Day 5) | Follow Up (Week 5) |
| Inclusion and Exclusion Criteria | NA | X | X |  |  |  |
| FSH Pathology | NA |  | X |  |  |  |
| TMS Adult Safety Screen Questionnaire | NA |  | X |  |  |  |
| Telephone Montreal Cognitive Assessment | NA |  | X |  |  |  |
| EEG Measures | Neurocognitive |  |  | X | X | X |
| TMS Measures | Neurocognitive |  |  | X | X | X |
| Heart Rate Variability | Autonomic |  |  | X | X | X |
| Skin Conductance | Autonomic |  |  | X | X | X |
| Blood Collection | Biochemical |  |  | X | X | X |
| Memory and Cognitive Confidence Scale | SCCs |  |  | X | X | X |
| Rey Auditory Verbal Learning Test | Verbal LearningVerbal Memory |  |  | X | X | X |
| D-KEFS Verbal Fluency | Verbal Fluency |  |  | X | X | X |
| Symbol Digit Modality Test | Processing Speed |  |  | X | X | X |
| Paced Serial Addition Test | Working Memory |  |  | X | X | X |
| Conners Continuous Performance Test-3 | Sustained AttentionVigilance |  |  | X | X | X |
| Visual Analogue Scale to Evaluate Fatigue Severity | State Fatigue |  |  | X | X | X |
| Patient Health Questionnaire-9 | Depression |  | X | X | X | X |
| General Anxiety Disorder-7 | Anxiety |  |  | X | X | X |
| Pittsburgh Sleep Quality Index | Sleep Quality |  |  | X | X | X |
| Menopause-Specific Quality of Life | Quality of Life |  |  | X | X | X |

# Introduction

## Study Rationale

Given the prevailing concerns around the lack of treatments for the cognitive and psychological symptom profiles associated with menopause, coupled with a lack of understanding of the underlying mechanisms, effective alternatives that can support females in the late menopause transition are urgently needed. iTBS may be a safe and effective therapeutic option to rescue the cognitive deficits and improve the psychological symptoms associated with the menopause transition. Findings from this pilot clinical trial have the potential to advance our understanding of the underlying mechanisms that affect cognition and mood in menopause and offer the potential for new non-invasive treatments to mitigate symptoms. Downstream outcomes and innovations from this research may improve the experience of the 80,000 Australian women who move into the menopause transition each year and mitigate the financial impacts of untreated menopause symptoms on the workforce.

## Menopause

Menopause is defined as the permanent end of the menstrual cycle. Menopause reflects oocyte depletion, cessation of ovarian follicular activity and gonadal steroid production, and reproductive senescence [1]. Menopause is generally diagnosed when menstruation has ceased for at least twelve consecutive months, occurring in the absence of any other pathological or surgical explanation for the cessation in menstruation [1]. The majority of females reach menopause between the ages of 45 and 55 [8], and the average age of menopause in Australia is 51 [9]. However, age at menopause is variable and is influenced by factors including gynaecological comorbidities, diet and exercise, smoking status, ethnicity and genetics, and socio-economic background [8, 10, 11].

Menopause is preceded by a midlife neuroendocrine ageing transition termed ‘the menopause transition’ [1]. The menopause transition is characterised by the gradual depletion of oocytes, changed levels of receptiveness to gonadal steroid feedback, wide hormonal aberrations, and irregular menstrual cycles [1]. To ensure uniformity in the terminology describing the transition, the Stages of Reproductive Aging Workshop +10 (STRAW +10) Criteria were formulated based on menstrual bleeding patterns to represent a consensus staging system for the menopause transition [12]. The transition has been characterised into late reproductive stage (-3), early menopausal transition (-2), late menopausal transition (-1), final menstrual period (0), and early postmenopause (+1) [12].

In the context of this pilot clinical trial, menopause will be considered as females who are undergoing spontaneous menopause not related to hysterectomy or oophorectomy (termed surgical menopause), or any other pathological explanation for the cessation of menstruation.

## Endocrinological Changes in the Menopause Transition

During the menopause transition, the hypothalamic-pituitary axis is known to lose sensitivity to feedback by oestrogens, leading to anovulatory menstrual cycle patterns [1]. Circulating levels of oestradiol, follicle stimulating hormone (FSH), and luteinising hormone (LH) can vary during the early stages of the menopause transition [1]. The selective, gradual decline in the follicular phase inhibin B hormone leads to a subsequent rise in FSH [8]. Rising levels of FSH occur at the same time as the accelerated loss of follicles from the ovary [13]. The changes in hormones during the early stages have been attributed to the decline in the number of oocytes [14, 15]. The subsequent cessation in ovarian follicular activity can activate the feedback mechanism in the hypothalamus-pituitary-ovarian (HPO) axis, leading to changed levels of gonadotropins [14, 15]. The hormonal aberrations are associated with anovulatory menstrual cycles. Eventually, menstruation ceases entirely [8].

Oestradiol is not affected until late in the menopause transition, as rising gonadotropins are thought to maintain serum concentrations [8]. Specifically, the elevated levels of FSH can maintain and increase oestradiol concentrations over the early stages of the transition [16]. Changes in hormonal concentrations result in the shortening of the menstrual cycle length during the early transition, followed by longer gaps between menstrual cycles over time [8]. Furthermore, circulating androgens, including testosterone, are not affected during the early menopause transition, which can lead to changes in the ratio between oestrogens and androgens and symptoms of elevated androgenic steroids in females [15].

## Menopause Symptoms and Mechanisms

The symptom profile in menopause is well-defined and primarily concerns vasomotor, cognitive, mood, and sleep complaints, as well as mechanistic factors like bioenergetic changes in the brain. The menopause transition is also associated with greater cardiovascular risk burden [17], genitourinary symptoms including atrophy of the lower genital tract [18], decreased libido [19], and increased rate of bone resorption [20]. Vasomotor complaints are a measure of autonomic nervous system dysfunction and are the most commonly reported menopausal symptoms, including a sudden increase of blood flow to the chest, neck, and face, sensations of excessive heat, and profuse sweating [21]. Survey data show that the most common menopausal complaints reported are hot flushes (72 %), sleep disturbances (64 %), and night sweats (58 %) [4]. Autonomic dysfunction in the menopause transition is extensively researched and highlights the evidence-practice gap regarding other common menopause symptoms. The cognitive and mood symptom profiles associated with menopause are less prioritised in research and clinical management in terms of mechanisms and potential treatments. For these reasons, the cognitive and mood symptoms associated with the menopause transition will be prioritised in this pilot clinical trial.

### Cognitive Symptoms

Females experiencing the menopause transition often report cognitive challenges. Between 62–67 % of females report subjective cognitive complaints (SCCs) during the menopause transition, including challenges with concentration, memory, planning, and ‘brain fog’ [2]. Alongside SCCs, studies have reported that females living with menopause, in comparison to reproductive-age females, have objective and measurable deficits in working memory, verbal memory, and other executive functions [3]; reduced frontal cortical volume may be driving changes in executive functions [22]. Importantly, data has demonstrated a link between the objective and subjective cognitive deficits reported throughout the menopause transition [23, 24]. SCCs are associated with an objective decline in performance of verbal memory and attentional processes during the menopause transition [23]. Certain domains of cognition, including verbal memory, working memory, and attention, are most affected by the menopause transition [4, 25-29]. A longitudinal study in midlife females (*n* = 2,411; mean age 51 years at first assessment) found that immediate and delayed verbal episodic memory recall and processing speed decreased in the menopause transition [25]. Serum levels of FSH and LH are correlated with changes in verbal episodic memory tests [25]. These findings are replicated in a similar study with reproductive-age females, perimenopausal females, and postmenopausal females that reported age-independent menopause effects on verbal function, and a correlation between verbal measures, oestradiol, and FSH [28]. Deficits in verbal memory and verbal learning have been linked to the slowing of complex information processing speed [4]. There is also evidence to suggest that the cognitive deficits seen in the transition can normalise in the postmenopause period [30]. The cognitive symptoms associated with the menopause transition are often overlooked in terms of importance and should be prioritised in future research as they can majorly impact activities of daily living and quality of life during the menopause experience.

### Proposed Mechanisms for Cognitive Symptoms

Cognitive deficits in the menopause transition have been associated with the lowered production of oestrogens [31]. This is most likely due to the ability of oestrogen to interact with neurotransmitter systems, modulate neurogenesis and synaptic plasticity, and affect cognitive function [32]. A preclinical study in oophorectomized rats found that oestradiol administration can induce rapid increases in hippocampal neuron potentiation [33] and increased levels of choline acetyltransferase in the hippocampus and frontal cortex [34]. It has been historically considered that the mechanisms behind the cognitive deficits reported in the menopause transition are likely hormonal. However, the cognitive symptoms seen in menopause may also be explained by hormone-mediated changes in brain metabolism.

The menopause transition is a neuroendocrinological process that can impact the ageing trajectories of numerous organ systems, notably the brain [5]. Gonadal sex hormones are known mediators of neural function, characterising menopause as a neurological transition state [35]. Characterisation of the menopause transition in the brain via molecular, cellular, and systems biological pathways demonstrates the broad impact that oestrogen depletion can have on neural processes [35], including alterations in bioenergetic gene expression, glucose metabolism, morphology, neuronal density, spinogenesis, and synaptogenesis [5, 35, 36]. Oestrogen depletion has also been linked to the increased deposition of amyloid-beta (Aβ) plaques in the brain in female mouse models, a key pathological hallmark of Alzheimer’s disease (AD) [37, 38]. Despite the recent understanding that brain bioenergetics may play a major role in mediating the cognitive deficits seen in menopause, this avenue has not yet been explored in terms of treatments.

An emerging field of research is focused on exploring changes in brain structure, energy utilisation, and connectivity across all stages of the menopause transition [5]. A recent multi-modal neuroimaging study recruited premenopausal, perimenopausal, and postmenopausal females to investigate changes in brain biomarkers across the menopause transition [5]. Findings showed that the menopause transition significantly impacts white matter structure, energy utilisation and metabolism, and connectivity in regions involved in higher-order cognitive functions [5]. Comparison with age-matched male controls showed that changes in regions sub-serving cognitive processes were specific to menopausal endocrine ageing as opposed to chronological ageing [5]. A second study found that reduced glucose metabolism in AD-vulnerable regions of the brain was correlated with a reduction in mitochondrial cytochrome C oxidase (COX) activity in perimenopausal and postmenopausal females [39]. Preclinical research has found that the hormonal transition from regular to irregular menstrual cycling is characterised by a reduction in bioenergetic gene expression, confirmed by a decline in glucose metabolism, mitochondrial function, and long-term potentiation (LTP) [6]. Additionally, the menopause transition is associated with distinct changes in electroencephalogram (EEG) activity during sleep that are not detected on other polysomnographic measures [40]. Elevated beta EEG power during sleep in females experiencing the late menopause transition and postmenopause suggests a pattern of hyperarousal and provides a measure of disturbed sleep quality [40]. These data support the hypotheses that brain bioenergetics and neurocognitive changes may be important underlying mechanisms to target when developing novel treatment options for menopause symptoms during the menopause transition.

Brain imaging analyses in humans have indicated that the neuroendocrine changes in the menopause transition can retain their influence even after the menopause transition is complete [5]. Potential adaptive compensatory processes have been observed, as *in vivo* brain mitochondrial adenosine triphosphate (ATP) production and grey matter volume (GMV) recovery correlated with the protection of cognitive performance postmenopause [5]. Brain imaging studies in postmenopausal females show atrophy in GMV compared to age-matched males, which has been linked to the development of cognitive impairments, and reduced glucose metabolism in the brain [5]. Females with genetic risk factors for neurodegenerative diseases (e.g., apolipoprotein epsilon-4 [APOE-e4]) also show lower GMV and glucose metabolism during the menopause transition, as well as increased deposition of Aβ [41]. Importantly, there is a paucity of data in this research space that limits the ability to develop treatments that can effectively remediate symptoms.

### Psychological Symptoms

Mood complaints are common in the menopause transition and have been linked to fluctuations in central nervous system (CNS) neurotransmitters, such as serotonin, dopamine, norepinephrine, and endorphins [42]. Data from the Study of Women’s Health Across the Nation demonstrated a marked link between poor sleep and hot flushes, depression, anxiety, and lower levels of oestrogen [43]. Survey data suggest that 47 % of menopausal females report feeling depressed, and 37 % suffered from anxiety [4]. Females with a lifetime history of depression are at risk of future depression with respect to the menopause transition [44]. Females without a pre-existing history of depression are also at risk during the menopause transition, with a 16 % prevalence of new onset depressive symptoms and/or anxiety [44]. Longitudinal studies have also demonstrated that a longer transition period is associated with depressive symptoms, likely due to increased duration of symptoms [45]. Anxiety levels are also affected by the menopause transition. Females with low anxiety levels at baseline are more susceptible to high anxiety during and after the transition, while females with high anxiety levels at baseline are prone to becoming more anxious during the transition [46].

### Proposed Mechanisms for Psychological Symptoms

There are various mechanisms by which the mood symptoms of menopause may occur. Changes in the concentrations of hormones are linked to the dysregulation of gamma amino butyric acid (GABA) balance, which is thought to increase the risk of depression and anxiety during midlife [47]. Distinct neurophysiological changes have also been observed in menopausal females experiencing depressive symptoms [48]. For instance, low oestradiol levels in females experiencing menopause have been linked to decreased vigilance, which can contribute to depressive symptoms [48]. Right frontal hyperactivation and left frontal hypoactivation have also been correlated with depressive symptoms in menopause [48]. It is worth noting that vasomotor symptoms have been associated with the new onset of depressive mood symptoms [49]. However, studies have not been able to demonstrate a reciprocal relationship between vasomotor symptoms and new onset of major depression [49, 50]. Despite the various mechanisms described in the literature, pharmacological treatments for mood symptoms are neurotransmitter-focused and do not address the potential neurophysiological mechanisms that have been reported.

The neurological changes seen in menopause, including deficits in cognition, changes in mood, and brain hypometabolism, may explain the increased risk of multifactorial hypometabolic conditions like dementia in females [6]. Prevalence studies in the US, Europe, and Australia have shown that dementia is almost twice as common in females than males [51-54], and it is the leading cause of death in Australian females over the age of 65 years [53]. The increased prevalence and incidence of dementia in females may be due to reduced levels of oestrogen [55], which has been found to exert tissue-specific effects and have a role in healthy ageing, cognition, and AD neuropathology [31]. Depressive symptoms, like those experienced by females experiencing the menopause transition, are also recognised as risk factors for developing dementia [56]. Research into the neurological and bioenergetic changes observed during menopause is ongoing, and no treatments or management strategies that tackle these underlying mechanisms have been proposed to date.

## Managing Menopause Symptoms

Majority of the treatment options for managing menopause symptoms focus on vasomotor symptoms, including hot flushes. The international 2023 Practitioner’s Toolkit for Managing Menopause [57] notes the most robust Clinical Practice Guidelines support menopausal hormone therapy (MHT) as the most effective treatment to improve vasomotor symptoms [58-60]. Extensive research has been conducted into the regulation of autonomic dysfunction in menopause. However, the cognitive and mood symptoms observed in the menopause transition are often considered secondary to vasomotor symptoms, despite their profound impacts on activities of daily living and quality of life. There are therefore limited treatment options for effectively managing the cognitive and psychological symptoms of the menopause transition.

It is unclear whether MHT can result in improved cognitive function in females. A recent systematic review and meta-analysis conducted a multi-level meta-regression to derive standardised mean difference and 95 % confidence intervals from 34 RCTs focused on exploring the efficacy of MHT for cognition (*n* = 14,914 [active] and *n* = 12,679 [placebo]) [61]. Data suggest that associations between cognitive function and MHT varied by treatment timing and drug formulation [61]. Importantly, MHT had no overall effects on all cognitive domain scores measured [61]. Oestrogen therapy, when initiated in the early stages of the menopause transition, was associated with improved verbal memory, however the same effect was not observed when oestrogen therapy was initiated in females aged over 65 years (late-life) [61]. Interestingly, oestrogen-progestogen therapy initiated in late-life populations was associated with a decline in Mini Mental State Exam (MMSE) scores when compared to placebo [61]. Oestrogen-progestogen therapy was associated with improved verbal memory in late-life, but not in midlife [61]. Duration of MHT treatment exceeding one year was associated with worsening visual memory [61]. The time-dependent effects of MHT on certain cognitive domains, varying based on formulation and initiation of treatment, emphasises the need for research into alternative therapies for cognitive deficits in the menopause transition. Furthermore, systematic reviews and meta-analyses of randomised controlled trials (RCTs) found no benefit of oestrogen therapy (oestrogen alone or coupled with progestogen), in postmenopausal females for menopause-associated depressive symptoms and anxiety [62]. Scant data have suggested that MHT may alleviate the depressive symptoms and anxiety seen in perimenopausal females [62], although the data to support this are limited [57].

MHT is also associated with specific adverse drug reactions (ADRs), including bleeding and spotting, breast tenderness, uterine fibroids [63]. The five-year breast cancer risk associated with MHT use is low in most females (< 3 %), however, MHT should not be prescribed in females with a high risk of breast cancer (> 6 %) [64]. Concerns regarding breast cancer risk are commonly communicated in the media and in the community [65]. Postmenopausal females seek information regarding the risks of MHT from magazines and newspapers (49 %), and television and radio (32 %); with only 28 % of females discussing risks with their doctor [66]. This is reflected in international surveys that characterise perceptions of MHT [66]. The most frequently mentioned concern of MHT in postmenopausal females is breast cancer (62 %), followed by concerns of cancer in general (22 %), and potential unknown side effects (17 %) [66]. In the subgroup of females who report using non-hormonal treatments to manage their symptoms, the primary aversion to MHT is the increased risk of breast cancer (34 %), with 57 % of females in this subgroup would not feel confident using MHT even if advised by a physician [66]. Risk of breast cancer and receiving negative news about MHT are commonly cited as reasons for stopping MHT treatment [66]. Considering the perception of MHT-related risks in the community, and scant data supporting effectiveness for treating cognition and mood changes, future research into alternative therapies is necessary.

## Transcranial Magnetic Stimulation (TMS)

The lack of treatments available for managing the cognitive and psychological symptom profile of menopause, coupled with the elevated risk of cerebral hypometabolic conditions and concerns about MHT use, warrants research into novel treatment options. Transcranial magnetic stimulation (TMS) is a neurostimulation and modulation technique of the brain, delivered via the non-invasive electromagnetic initiation of an electric field [67]. During TMS, an electromagnetic coil is placed over a target region in the scalp and the magnetic field passes through the skull in accordance with Faraday’s law [67]. The induced electric field can be of satisfactory density and magnitude to induce a secondary electrical current in the underlying cortical tissue by depolarising neurons and initiating action potentials [67]. When applied to target regions of the brain, the peripheral response to TMS can provide insight into the integrity and excitability of specific central nervous system pathways [67]. For this reason, TMS is often applied to study brain-behaviour relations and the pathophysiology of numerous psychiatric and neurological disorders [68-74]. TMS-induced modulation of cortical excitability in specific cortico-subcortical networks is known to persist post-intervention, leading to controlled behavioural changes, underscoring the therapeutic potential of TMS [67]. Furthermore, TMS is considered a safe and tolerable intervention [75].

### Repetitive TMS (rTMS)

Repetitive TMS (rTMS) refers to applying recurring TMS pulses to a specific region of the brain [7]. rTMS has been broadly classified as either high frequency (>1 Hz), or low frequency (<1 Hz) [7, 76]. Early literature reported that the high frequency paradigm (>1 Hz) can increase cortical excitability and consists of a burst of stimuli that normally last for up to 10 seconds, separated by pauses of 30–60 seconds [77]. The low frequency paradigm (<1 Hz) can depress cortical excitability and consists of continuous trains of single pulses [77]. However, studies have acknowledged inter-individual and intra-individual variability in terms of cortical responses [78]. The risk of rTMS-related seizures remains low [79] and has been reported to have a standardised risk of 7/100,000 sessions [80]. There is a very low incidence of adverse effects associated with rTMS when participants are appropriately screened [67]. These data suggest that rTMS is an acceptable and non-invasive treatment for multiple symptom profiles, including cognition and mood.

rTMS has been found to be a promising non-invasive treatment for the symptoms associated with a variety of psychiatric and neurological disorders [67], including treatment-resistant depression (TRD) [67], anxiety [81], neuropathic pain [82], musculoskeletal pain [83], Parkinson’s disease [84], and AD [85-87]. In 2008, rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) was approved by the US Food and Drug Administration (FDA) for treating major depressive disorder (MDD). The DLPFC is a core region involved in executive functions [7]. The FDA then approved multiple devices, and amended the rTMS device’s indication to target TRD [7]. The non-invasive nature of the treatment and its low side effect profile suggests that rTMS may be of high clinical utility for treating the cognitive and mood symptom profiles in menopause.

### Clinical Utility of rTMS for Improving Cognition

Various meta-analyses have supported the use of rTMS to improve cognition in multiple cohorts, including healthy adults and people with cognitive impairments [88]. Two recent meta-analyses have demonstrated that high frequency rTMS can improve cognition in healthy cohorts [88, 89]. Additionally, a further two meta-analyses have shown that high-frequency rTMS to the DLPFC can significantly improve memory [85, 87]. The characteristics and findings of these key meta-analyses are reported in Table 2.

**Table 2.** Summary of key meta-analyses assessing the efficacy of rTMS on cognition in healthy and clinical populations.

|  |  |  |  |
| --- | --- | --- | --- |
| Citation | Cohort | Population | Summary of Findings |
| Patel et al., 2020 [88] | Healthy | *N* = 15*n* = 252 | * High frequency rTMS improved executive functioning
* Low frequency rTMS improved episodic memory and visual perception
 |
| Xu et al., 2024 [89] | Healthy | *N* = 53*n* = 1507 | * High frequency rTMS improved accuracy and reaction across all domains
* Greater effects reported for executive functioning
 |
| Chou et al., 2020 [85] | AD, MCI | *N* = 13*n* =239 | * Active rTMS can improve cognitive function
* High frequency rTMS over the left DLPFC and low frequency rTMS over the right DLPFC improved memory
* High frequency rTMS over the right inferior frontal gyrus improved executive performance
* The effects of rTMS persisted for 4–12 weeks post-treatment
 |
| Zhang et al., 2022 [87] | AD | *N* = 9*n* = 361 | * High frequency rTMS to the left DLPFC improved cognition
* The effects of rTMS persisted for over 4 weeks post-treatment
 |
| Note. *N* refers to number of studies, while *n* refers to number of participants. |

### rTMS Mechanisms for Improving Cognition

There are various potential mechanisms that may explain the therapeutic effects of rTMS for cognitive function [90]. Preclinical models of dementia have shown that daily high-frequency [91-93] and low-frequency [92, 94-96] rTMS (for 2–4 weeks) can improve hippocampal-dependent functions in memory and learning [90]. Several preclinical and clinical models have shown that rTMS is able to improve neural plasticity by restoring LTP deficits [97, 98]. Treatment with rTMS can modulate hippocampal LTP by facilitating the large-conductance of calcium-activated potassium channels, thereby decreasing cortical excitability [99]. The enhanced synaptic function induced by rTMS could also be due to the elevated expression of neurotrophic factors brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor in the hippocampus [93, 100]. rTMS is also known to increase neurogenesis in the dentate gyrus [101] and promote neurogenesis by upregulating the expression of the neuroprotective cholecystokinin [102]. It is thought that the various molecular and cellular mechanisms by which rTMS rescues cognitive function interrelate to produce network-level brain function changes that are observable in healthy and clinical cohorts.

### Clinical Utility of rTMS for Improving Mood

Various systematic reviews and meta-analyses support the efficacy and acceptability of rTMS for treating major depression in both clinical and preclinical studies [103-105]. A systematic review and meta-analysis of RCTs (*N* = 29; *n* = 1371) reported that high-frequency rTMS is associated with clinically relevant antidepressant effects [104]. Data show that rTMS is effective as an augmentation strategy and a monotherapy for bipolar depression and primary unipolar depression [104]. A systematic review and meta-analysis of the use of rTMS to treat anxiety (*N* = 6; *n* = 152) reported a robust effect in the context of limited and heterogenous studies [106]. Numerous studies have investigated the neurobiological mechanisms by which rTMS can improve mood [107], although there are difficulties converging the findings due to the large variety of rTMS parameters reported. There is generally an understanding that rTMS can exert therapeutic effects for mood in a frequency-dependent matter by altering neurotransmitters, electrophysiology, and blood flow in the brain [107].

### rTMS Impacts on Immunological Function

Data suggests that rTMS treatment can affect serum inflammatory cytokine levels in people living with depression [108]. A preliminary study exploring the characteristics of inflammatory cytokines in people living with depression at 2- and 12-weeks post-rTMS intervention reported multiple dynamic changes in cytokine profiles [108]. Active rTMS treatment was associated with increases in serum levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin-2 (IL-2) at 2-weeks post-intervention, and these changes persisted to the 12-week mark [108]. Improved depressive symptoms were associated with a reduction in tumour necrosis factor-alpha (TNF-alpha) at 2-weeks and IL-2 at 12-weeks [108]. As the first study of its kind, these findings support the notion that rTMS has immunomodulatory capacities, resulting in changes to inflammatory cytokines; further research is required.

### rTMS Impacts on Autonomic Function

rTMS can impact autonomic functions. Studies have explored the clinical utility of non-invasive brain stimulation on physiological stress responses and heart rate variability [109]. High-frequency rTMS over the left DLPFC has been reported to help with attenuating physiological stress reactions, which is in line with the therapeutic indication of rTMS in affective disorders [110]. A similar study reported that high-frequency rTMS to the left DLPFC is associated with a lower cortisol response to stress [111]. Together, these findings suggest that rTMS is an effective tool to investigate the cortical regulation of autonomic nervous system and potentially treat autonomic dysfunction in females [109].

### Interactions Between rTMS and Sex Hormones

Sex hormones are known to impact TMS-measures of cortical excitability [112]. A systematic review assessing the effects of hormonal treatments and sex hormones showed that endogenous oestrogen, progesterone, and testosterone can have modulatory effects on TMS-measured cortical excitability [112]. Higher levels of oestrogen and testosterone are associated with greater cortical excitability, and higher levels of progesterone are associated with lower levels [112]. Menopausal status and ovarian hormone levels are known to impact rTMS interventions for TRD [113]. A study investigating the antidepressant efficacy of rTMS (premenopausal females *n* = 17; postmenopausal females *n* = 15; males *n* = 16) investigated the effect of sex hormones [113]. Data found no differences in the rTMS response rate between premenopausal female and male patients [113]. Importantly, postmenopausal female patients responded the least (0 %) [113]. This finding is replicated in a second study which showed that 0 % of postmenopausal females with TRD responded to adjunctive rTMS [114], suggesting that rTMS is not an effective treatment for mood symptoms in postmenopausal females.

rTMS responsivity in women experiencing the menopause transition has been related to reciprocal interactions between sex hormones and rTMS mechanisms of action. Greater improvements in depression scores were associated with a higher oestradiol/progesterone ratio in premenopausal females [113]. Regression analyses found that ovarian steroid levels and menopausal status are the main predictors of rTMS efficacy in females [113]. Moreover, a systematic review has reported multiple mutual interactions between rTMS and sex hormones (*N* = 18, *n* = 415) [113]. Data show that the late follicular phase is associated with a weak intracortical and between hemispheric inhibition, strong intracortical facilitation, and high stimulation-induced behavioural and neural changes; while the opposite effects were observed during the luteal phase [113]. The repetitive application of non-invasive brain stimulation is also known to increase oestradiol and dehydroepiandrosterone (DHEA) levels in neurological cohorts [113], including Parkinson’s disease and disorders of consciousness [115]. Importantly, these data suggest that hormonal processes can modulate brain activity, and that the modulation of cortical activity via brain stimulation can impact hormonal processes. These data suggest that the early or late menopause transition may be the ideal time to intervene, given the lack of effectiveness of rTMS in improving mood symptoms in postmenopausal females.

Despite the data demonstrating that rTMS may have clinical utility in treating cognitive and mood changes in various cohorts and the capacity for reciprocal interactions with neuroendocrine processes, no such study has been conducted to explore the therapeutic potential of rTMS in managing the cognitive symptom profile throughout the menopause transition.

### Theta-Burst Stimulation (iTBS)

While rTMS interventions are associated with acceptable efficacy, remission, and drop-out rates in clinical cohorts [116], there are feasibility challenges associated with the daily rTMS sessions applied in a standard course of treatment. Daily treatments are considered time-consuming and taxing for patients, clinical trial participants, and healthcare services. Furthermore, observations within clinical settings suggest that improved symptoms are typically observable within 10–20 sessions [117], suggesting that patients can experience distress before experiencing symptom improvement [118]. The practical challenges associated with daily attendance over multiple weeks, coupled with the time required before the improvement of clinically observable symptoms, are relevant limitations of rTMS that can limit clinical trial recruitment and retention.

The practical limitations of rTMS in clinical trial settings can be remedied by using theta-burst stimulation (TBS) protocols [118]. TBS protocols are a form of rTMS treatment that can be used to up-regulate or down-regulate excitability in the cortex by mimicking the natural firing patterns of the brain [119-121]. Intermittent patterns of TBS (iTBS) are known to induce long-term potentiation (LTP) in targeted neural circuits and increase excitability within targeted neural circuits [122]. iTBS protocols are used commonly and considered advantageous as they can be applied quickly (40–190 seconds), relative to rTMS protocols (which can last up to 30 minutes) [123].

Various meta-analyses have described iTBS use to improve cognition and mood in multiple cohorts, including healthy adults and people with cognitive impairments. Key data are summarised in Table 3. Briefly, these meta-analyses show that iTBS can improve cognition [124, 125] and mood [126, 127], although there is a significant amount of study heterogeneity [124, 125].

**Table 3. Summary of key meta-analyses assessing the use of iTBS on cognition and mood in healthy and clinical populations.**

|  |  |  |  |
| --- | --- | --- | --- |
| Citation | Cohort | Population | Summary of Findings |
| Pabst et al., 2022 [124] | Healthy | *N* = 50*n* = 1461 | * iTBS may enhance cognition in healthy cohorts
* There is a significant amount of heterogeneity across studies
 |
| Zheng et al., 2024 [125] | Cognitive dysfunction | *N* = 12*n* = 506 | * iTBS treatment showed a trend toward improvement of total cognitive function and activities of daily living
* Quality of evidence remains low
 |
| Kishi et al., [126] | Depression | *N* = 23*n* = 960 | * iTBS over the left DLPFC had a higher response rate when compared to sham
* iTBS over the left DLPFC led to the most significant depression symptom improvement when compared to other TBS protocols
 |
| Cai et al., 2023 [127] | Depression | *N* = 5*n* = 239 | * Accelerated iTBS was significantly superior to sham iTBS for response, but not for remission
 |
| Note. *N* refers to number of studies, while *n* refers to number of participants. |

Despite the data demonstrating that iTBS may have clinical utility in treating cognitive and mood changes in various cohorts and the data demonstrating the capacity of rTMS to have reciprocal interactions with neuroendocrine processes, no such study has been conducted to explore the therapeutic potential of iTBS in managing the cognitive symptom profile throughout the menopause transition. The proposed PhD project will address this research gap.

## Study Aims and Objectives

The aim of this PhD project is to assess the underlying mechanisms of action of iTBS in females in the late menopause transition, and to assess the relationship with cognition and mood. To accomplish this, the PhD project will involve a randomised, sham-controlled, double-blinded pilot clinical trial comprising four empirical studies that map onto each of the four objectives.

Specific objectives of this PhD are listed below and are specific to the late menopausal transition stage:

**Objective 1 (Study 1)**: Characterising the potential neurocognitive mechanisms of iTBS.

**Objective 2 (Study 2)**: Characterising the potential autonomic mechanisms of iTBS.

**Objective 3 (Study 3)**: Characterising the potential biochemical mechanisms of iTBS.

**Objective 4 (Study 4)**: Exploring a possible signal of efficacy via effect-size estimates of changes in cognitive and mood outcomes.

# Methodology

## Study Design and Intervention

The research will be conducted in the form of a randomised, controlled, double-blind pilot clinical trial. Participants will receive five sessions of iTBS over the left DLPFC. iTBS will be delivered using a MagVenture Transcranial Magnetic Stimulator (MagVenture A/S DK-3520, Denmark). The coil will be held tangential to the scalp with the handle pointed posterolaterally away from the midline at 45 degrees to induce a second phase current in the posterolateral to anteromedial direction [128]. Resting motor threshold (rMT) will be determined as the lowest stimulation intensity at which 5 out of 10 TMS pulses produce a visible response in the first dorsal interossei muscle of the right hand. Stimulation intensity will be delivered at 90 % of the rMT, which will be assessed at the start of each rTMS session [129]. The TMS coil will be positioned through a Brainsight neuro-navigation system (Rogue Research Inc., Canada) based on anatomical landmarks in MNI space [130]. The coil will be positioned over the left DLPFC in accordance with the BeamF3 algorithm. The left DLPFC was chosen as a core region involved in executive functions, and the FDA has approved rTMS for the treatment of affective disorders targeting the region [7].

Following randomisation, participants will be allocated to one of the two trial arms (sham or active treatment). Active treatment will consist of five sessions of iTBS over five consecutive days. Participants will receive five blocks of iTBS, and each block will be separated by ten minutes [131]. Bursts of three pulses will be delivered at 50 Hz, repeated at 200 millisecond intervals in trains of two seconds [131]. Two-second trains of iTBS will be repeated every ten seconds for a total of 600 pulses per block, and 3000 pulses per session [131].

The sham condition will involve the use of a coil that reproduces the audible click of the active iTBS without applying any stimulus. The sham condition will follow the same protocol as the active treatment. Briefly, the sham condition will consist of five blocks of iTBS each day over five consecutive days, and each block will be separated by ten minutes. Two-second trains of iTBS will be repeated every ten seconds for a total of 600 pulses per block, and 3000 pulses per session. Importantly, no stimulus will be applied to the scalp.

## Study Population

This pilot clinical trial will recruit females in the late menopausal transition stage (Stage -1 according to the STRAW +10 Criteria [12]). This cohort was chosen for two primary reasons: (a) there is evidence to suggest that the cognitive deficits reported are most pronounced during the late menopause transition and can normalise in the postmenopause period [30]; and (b) rTMS treatment responsivity in females with mood disorders is associated with a higher oestradiol/progesterone ratio [113].

The late menopausal transition stage is marked by the occurrence of amenorrhea of 60 days or longer [12]. Menstrual cycles are significantly affected at this stage, characterised by extreme fluctuations in hormonal levels, increased variability in cycle length, and the increased prevalence of anovulation [12]. Females experiencing the late menopausal transition stage often exhibit elevated FSH levels in associated with high oestradiol levels [12]. Vasomotor symptoms are also likely to occur during this stage [12], meaning many females will seek treatment and commence MHT at this stage [132].

## Inclusion and Exclusion Criteria

Proposed inclusion criteria are as follows:

* Females undergoing the late menopausal transition stage according to the STRAW criteria as defined by: (a) amenorrhea of 60 days or longer; (b) FSH levels greater than 25 IU/L in a random blood draw; and (c) self-reported vasomotor symptoms, including hot flushes, sleep disturbances, and night sweats [12].
* Females experiencing self-reported subjective cognitive complaints relative to previously normal cognitive status [133, 134]; and self-reported depressive symptoms or anxiety.
* Willing to complete all study-related activities for the complete trial including in person assessments and remote follow-ups.

Proposed exclusion criteria are as follows:

* Individuals who have contraindications to TMS identified using the Transcranial Magnetic Stimulation Adult Safety Screen questionnaire [135], including:
1. History of adverse reactions to rTMS or other forms of non-invasive brain stimulation such as transcranial direct current stimulation (tDCS) [136].
2. History of seizures, a medical diagnosis of epilepsy, or family history of epilepsy [136].
3. History of strokes, head injuries with loss of consciousness > 30 min, severe dizzy spells, or frequent or severe headaches and/or migraines [136].
4. Individuals with metal inside the head (outside of the mouth), including shrapnel, surgical clips, or fragments from welding or metal works [136].
5. Individuals with any implanted devices such as cardiac pacemakers, medical pumps, intra-cardiac lines, or Cochlear implants; or with a fine-wire electrode inserted anywhere in their body [136].
* Reproductive age females; females in the late reproductive stage or the early menopausal transition; and postmenopausal females [12].
* Females who have been receiving MHT treatment for less than three months at the time of recruitment or plan to commence MHT treatment during the study duration.
* Individuals using neuroactive medications, including anticonvulsants, antidepressants, and anxiolytics [137].
* A diagnosis of neurodegenerative, psychiatric affective, non-affective, or neurological illness.
* Significant cognitive impairment as deemed by scoring 17 or less on the Telephone Montreal Cognitive Assessment (T-MoCA) [138].
* Current episode of major depression as deemed by scoring 15 or greater according to the Patient Health Questionnaire-9 (PHQ-9) [139].
* High dependence on medical care (including medications, particularly drugs with a narrow therapeutic index) due to past or current medical conditions (e.g., cancer) as deemed by the study physician.
* Study physician discretion regarding medical status, appropriateness of participation, or concern about intervention adherence.
* Individuals who are not willing to follow the study protocol e.g., are not able to attend face-to-face visits or those who plan to move out of the area or travel interstate or overseas within the treatment period.
* Individuals who are actively participating in another clinical trial(s).
* Individuals who are not proficient in reading and writing in English.

## Sample Size Determination

To the best of our knowledge, this research will be the first of its kind and therefore an accurate sample size determination is not possible. However, an exploratory sample size of 60 participants has been chosen to maximise feasibility and recruitment potential and characterise the potential mechanisms of iTBS. This sample size was determined based on previous mechanistic literature that focused on the stimulation of the DLPFC in healthy participants with no medical, neurological, or psychiatric history, and observed network-specific effects [140]. Additionally, this sample size exceeds the evaluations of previous rTMS and iTBS pilot studies that have observed improvements in cognitive function in various clinical groups, which range from 10 – 30 participants [141-146].

Mood-focused meta-analyses and key menopause-related studies suggest that rTMS response rates can vary from approximately 40–70 % [114, 147-150]. Importantly, a study that examined how gender and menopausal status contribute to age effects on the antidepressant efficacy of rTMS reported premenopausal female participants had a response rate of approximately 69 % [113]. Assuming a response rate of 69 %, a minimum of 40 participants will be allocated to the active arm. In relation to responders and non-responders, it is estimated that approximately 28 participants will be classified as responders and 12 participants as non-responders. This sample size will allow for sub-group analysis of mechanistic outcomes.

This sample size was calculated using the following calculator for binary sample sizes: <https://www.johndcook.com/binary_sample_size.html>. The calculator is based on the rule of thumb which assumes significance α = 0.05 and type II error β = 0.20 (80% power). Additionally, we are assuming a potential dropout rate of 20 % based on previous clinical trial experience. To factor in a dropout rate of 20 %, we will recruit an additional 12 participants (72 total) as needed.

## Recruitment Strategy

The primary recruitment strategy will use targeted social media advertising on the Meta platform, including Instagram and Facebook. Alternative recruitment channels include the research team’s community and professional networks, not-for-profit organisations, and advocacy groups such as Australasian Menopause Society (AMS), Jean Hailes etc. Advertisements for the trial will provide an overview of the trial and refer potential participants to the NICM Health Research Institute website (nicm.edu.au) for further information. Interested parties will be invited to complete a screening questionnaire to assess their initial eligibility for participation. Responses will be assessed by the research team and potential participants will be asked to schedule a phone call to confirm eligibility. Potential participants who are found to be eligible following the phone call will be referred to a commercial pathology service to receive a random blood-draw to check FSH levels. Upon confirmation that all inclusion criteria and none of the exclusion criteria have been met, participants will be enrolled into the study and randomised into either the sham or active group.

Participants will be offered reimbursement to cover travel expenses, for a total of $150.00. participants will be provided with on-site parking at Westmead and offered refreshments for face-to-face visits.

## Randomisation and Blinding

Randomisation will be facilitated using REDCap, allowing for both concealment and randomisation. Participants will be randomly allocated to receive rTMS or sham at a 2:1 ratio using randomly permutated blocks of 6 [151]. The trial will be double-blinded, meaning that all participants, members of the research team, and statisticians will be blinded to group allocation.

## Ethical Considerations and Informed Consent

Prior to commencement of the research, the research team will seek review from the Western Sydney University (WSU) Human Research Ethics Committee (HREC) for a greater-than-low risk clinical trial. The protocol, protocol amendments, Participant Information Sheet and Consent Form (PISCF), and other relevant documents (e.g., advertisements) will be submitted to the HREC by the team and reviewed and approved prior to the initiation of the study.

This pilot clinical trial will be recruiting people living with SCCs and/or symptoms of depression and recognises that there may be increased susceptibility to discomfort or stress amongst this cohort. The research design considers factors that may affect the capacity to receive information, to consent to research, or to participate in it. This is in line with Chapter 4.5.1 of the National Statement. The process of obtaining informed consent reflects this susceptibility. However, it is important to distinguish that the participants recruited for this clinical trial are healthy and have not been diagnosed with a concurrent neurodegenerative, psychiatric affective, non-affective, or neurological illness. Therefore, the project will consent the participant directly, and not a caregiver.

People with SCCs retain their functional independence and decisional capacity, unlike people with mild cognitive impairment or dementia (such as Alzheimer’s disease). Potential participants will be screened for general health and functional independence to ensure that people with a neurodegenerative or psychiatric diagnosis that may impede on their day-to-day function will not be included in the trial. Additionally, the study physician will maintain discretion regarding medical status, appropriateness of participation, or concern about intervention adherence. The study neuropsychologist will maintain discretion regarding cognitive status.

This clinical trial will collect informed, written, extended consent from all participants. Potential participants will be pre-screened via an online form prior to undertaking the consent process. Participants who are eligible as per the pre-screening process will be invited for a phone screening interview, followed by a pathology screening test. At this point, the investigator will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study. Potential participants will be informed that their participation is voluntary. If participants are found to be eligible, the participant will be enrolled and invited to the NICM Health Research Institute, where the informed consent process will take place face-to-face. Once initial consent has been obtained, participants will have the option to contact a study physician to revisit the informed consent process, confirm informed consent, and answer any medical-related questions the participant may have regarding participation in the trial. At all points during the screening and consenting process, refusal or reluctance to participate in the research project will be respected.

Participants must be reconsented to the most current version of the PISCF during their participation in the study. A copy of the PISCF must be provided to the participant. A participant who is rescreened is not required to sign another PISCF if the rescreening occurs within three months of the previous PISCF signature date, provided that a new PISCF has not been issues within that timeframe.

Some participants may share experiences or information which may be negative or distressing. Support and access to helpline numbers and/or counselling via the Participant Information Sheet will be provided. If participants remain distressed, we will encourage them to seek assistance through their primary physician that day.

## Study Flow and Testing

Study flow is depicted in Figure 1. Participants will be tested at three timepoints (baseline, endpoint, and follow up). Baseline testing will be conducted prior to the commencement of the intervention (Day 1). The iTBS intervention will be delivered over one week (Week 1). Endpoint testing will be conducted at the conclusion of the intervention period (Day 5). Follow up testing will be conducted at the precise four-week post-intervention mark (Week 5). Study duration will be five weeks in total.

****

**Figure 1. Study flow diagram.** Participants will receive either active or sham rTMS treatment. Follow up will occur at the precise four-week post-intervention mark. There will be three testing sessions in total: Baseline (Day 1), Endpoint (Day 5), and Follow Up (Week 5).

# Primary Estimands (Neurocognition)

Study 1 will focus on the neurocognitive mechanisms of rTMS in females in the late menopause transition. Cortical activity will be assessed via electroencephalography (EEG). Participants will be seated in an air-conditioned, dark, sound-attenuated room. Data will be acquired using the Compumedics Okti® 32-channel acquisition module (Victoria, Australia), a high-definition portable EEG amplifier. Participants will be fitted with Okti® EEG recording equipment and seated approximately 80cm from a 21-inch screen with a keyboard placed in front of them. Participants will first complete a brief electrooculogram (EOG) calibration task that will later be used for removal of EOG-related artefacts in the data [152]. For resting-state, participants will be instructed to focus on a grey cross centred on a black background, measuring 10 × 10 mm, to record their eyes open followed by eyes closed resting-state EEG for six minutes each [153, 154]. In both the EOG calibration and the resting-state, continuous electrophysiological data from 0−70 Hz will be recorded using the Compumedics CURRY® 9 digital signal-processing system (Victoria, Australia), referencing to Cz during active recording.

Resting-state EEG data will be EOG corrected using the Revised Artefact Aligned Average (RAAA) EOG Correction Program [155], re-referenced to digitally-linked mastoids, and then separated into 2 s epochs in Neuroscan Edit (Compumedics, Victoria, Australia). Epochs will be baselined by their average amplitude and submitted to automatic artefact rejection to remove epochs including artefacts exceeding ± 75 µV in any EEG channel, voltage jumps, and flatlines. The data will then be visually inspected to interpolate any bad channels and remove any remaining epochs featuring artefacts. Clean, resting state EEG activity will then be submitted to discrete Fourier transformation to convert data from the time to the frequency domain and obtain spectral amplitudes at 0.5 Hz resolution. The PaWNExtra algorithm will then be applied to obtain pink (1/*f*) and white noise estimates [156]. Aperiodic pink noise activity is a rapidly emerging area of and has been associated with ageing and executive function and is hypothesised to reflect underlying neurobiological processes including neural spiking rates and excitatory-inhibitory balance [157]. Aperiodic pink noise was chosen as a primary outcome has it has been associated with ageing and executive function [158, 159]. Additionally, they are hypothesised to reflect underlying neurobiological processes including excitatory-inhibitory balance [160].

# Co-Primary Outcomes (Neurocognitive Mechanisms)

Paired-pulse TMS will be used to investigate activity within intracortical circuits as a co-primary outcome. Intracortical inhibition will be measured via short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI). Short interval intracortical facilitation (SICF) and short latency afferent inhibition (SAI) will also be measured. These paradigms were chosen as they have been previously used to stage and predict functional decline in people living with frontotemporal dementia [161].

SICI, LICI, SICF, and SAI will be studied using a paired-pulse technique that employs a conditioning-test design. The test stimulus will be adjusted to evoke a motor-evoked potential (MEP) of 1 mv amplitude in the first dorsal interossei muscle of the right hand [161]. To measure SICI and ICF, the conditioning stimulus (CS) will be adjusted at 70 % of the RMT, and multiple interstimulus intervals (ISIs) will be employed. ISIs include 1, 2, 3, and 5 ms for SICI and 7, 10, and 15 ms for SICF. To measure SICF, the CS intensity will be set to 90 % of the RMT, and the CS will be delivered after the test stimulus (TS). ISIs include 1, 1.3, 2.1, 2.5, 3.3, and 4.1 ms. LICI will be investigated by implementing two supra-threshold stimuli, and the CS will be adjusted at 130 % of the RMT. ISIs include 50, 100, and 150 ms. SAI will be evaluated by employing a CS of single pulses of electrical stimulation to the right median nerve [161].

# Secondary Outcomes (Autonomic/Biochemical Mechanisms)

Changes in autonomic function will be assessed in Study 2 via skin conductance and heart rate variability (HRV) [162, 163]. Autonomic variables were chosen as previous studies have shown that rTMS can alter skin conductance and heart rate variability, and these variations are linked to behavioural changes [164]. Skin conductance will be recorded from the same resting-state protocol used for the EEG, using the Compumedics Okti® system and UFI Bioderm Model 2701 at 0.5V [165]. HRV will be measured using the Polar H10 sensor (Massachusetts, USA) through a six-minute eyes closed EEG task. All data will be stored on a Dell Optiplex 755 desktop.

Study 3 will focus on the biochemical mechanisms of rTMS in females in the late menopause transition, measured in serum samples that will be collected in-house. Venous blood will be collected from the ante-cubital area. One 10 mL SST™ II vacutainer collection tube and a vacutainer standard holder (Becton, Dickinson, and Company, USA) will be used to collect one 10 mL tube of whole blood from each participant. Blood samples will be weighed and centrifuged at 4°C to separate the serum. Serum (500 µL) will be aliquoted into 1500 µL Eppendorf tubes using 1000 µL pipette tips. The remainder of the biospecimen (e.g., blood cells and clotting proteins) will be disposed of in adherence with the appropriate SOPs, and the serum aliquots will be stored in a -80°C freezer. While DNA extraction is possible from serum, we will not perform any DNA characterisation that may lead to the identification of the donor.

Blood will be collected into and transported in unbreakable plastic containers that are specifically designed for biospecimen collection.  Biospecimens will be processed as per the Australian Standard “Packaging for surface transport biological material that may cause disease in humans, animals, and plants - AS 4834”.  Our samples fall under Category 2.6.3.2.3.8 “Human specimens for which there is minimal likelihood that pathogens are present” (Australian Dangerous Goods Code 7.9 2024 Edition).  These specimens will be stored in a triple packaging system that will prevent leakage and will be marked with the words “EXEMPT HUMAN SPECIMEN".  The researcher will wear approved medical-grade PPE for the duration of the biospecimen collection, handling, and analysis.  PPE will be worn as detailed in the University's Standard Operating Procedure for Storage of Biospecimens (SOP 1527-TRTS-V1, expiry date 30/5/2026).  Serum samples will be stored in the freezer located in Room J.1.16 (Asset No.: 2172852).

All enzyme-linked immunosorbent assays (ELISA) will be purchased from Abcam (Cambridge, UK). Inflammatory cytokines CRP, IL-2, and TNF-alpha will be measured in serum samples, as rTMS has been known to affect dynamic patterns of these markers in people living with depression and are known to be potential effect modifiers [108]. CRP will be measured in the serum using the Human CRP ELISA Kit. IL-2 will be profiled using the Human IL-2 ELISA Kit. TNF-alpha will be measured via the Human TNF Alpha ELISA Kit. We will also be measuring energetic markers in the serum, chosen based on the bioenergetic hypotheses of menopause [5]. ATP will be profiled using the ATP Assay Kit (Colorimetric/Fluorometric). NAD and NADH will be profiled using the NAD/NADH Assay Kit. Finally, we will be profiling neurometabolic and neuroimmune markers related to the kynurenine pathway (KP). The KP was chosen as key metabolites, including quinolinic acid, can predict treatment responsivity and efficacy following theta burst stimulation [166]. All reagents used will be of analytical mass spectrometry-grade and purchased from ChemSupply (NSW, Australia).

# Tertiary Outcomes (Cognition/Mood Effects)

The focus of Study 4 will be self-reported changes in SCCs, measured by the overall score of the MACCS [167]. The MACCS is a self-report measure consisting of four individual subscales: (a) General Memory; (b) Decision Making; (c) Concentration and Attention; and (d) High Standards. This scale has been found to have sufficient internal consistency for each subscale and the overall score [167]. This scale has been previously used in menopause populations. For instance, the MACCS was used to measure changes in SCCs following a cognitive remediation intervention for women during the menopause transition [167]. SCCs were selected as they are most commonly reported by females experiencing the menopause transition, and often associated with an objective decline in performance of verbal memory and future risk of cognitive impairment [22]. Additionally, comprehensive neurological assessments have shown no difference in objective cognitive performance between premenopausal females, females experiencing the menopause transition, and postmenopausal females [168]. However, females undergoing the menopause transition report significantly more SCCs and less contentment with their cognitive abilities when compared to pre- and postmenopausal females [168].

Other cognitive outcomes include objective changes in verbal memory, verbal learning, verbal fluency, psychomotor processing speed, working memory, and sustained attention and vigilance. Verbal learning and memory will be assessed via the Rey Auditory Verbal Learning Test (RAVLT) [169], which has been previously used in a study which assessed the relationship between SCCs and objective cognitive deficits in females experiencing the menopause transition, as well as contentment with their cognitive abilities [168]. The RAVLT also has multiple parallel forms, minimising the effects of repeated testing. Verbal fluency will be assessed via the D-KEFS Verbal Fluency (Letter Fluency and Category Fluency) [170], which has been validated in individuals aged 8 to 89 years and is accepted as a valid measure of fluent productivity in the verbal domain. Psychomotor processing speed will be assessed via the Symbol Digit Modality Test (SDMT) [171]. The SDMT has been validated in cohorts of similar age to those being recruited in this clinical trial, has acceptable test-retest reliability, and alternate forms [172]. Working memory will be assessed via the Paced Serial Addition Test (PASAT), which has high levels of internal consistency and test-retest reliability [173]. Sustained attention and vigilance will be assessed via the Conners Continuous Performance Test-3 (Conners CPT 3), a task-oriented computerised assessment with diagnostic confidence [174]. State fatigue before and after completing cognitive assessments will be assessed via the Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F), which places fewer restrictions on the range of responses available to participants, in contrast to other discrete scales [175].

The clinical trial will also assess the effects of an rTMS intervention on the psychological symptom profile as secondary outcomes, including depressive mood, anxiety, sleep quality, and quality of life. Depressive symptoms will be assessed via the Patient Health Questionnaire-9 (PHQ-9) [176], a brief depressive symptom scale. Individual patient data meta-analysis has shown that the PHQ-9 has greater sensitivity compared with semi-structured diagnostic interviews [176], and has been used in numerous menopause studies [177-179]. Additionally, items of the PHQ are closely aligned with the DSM diagnostic criteria for major depressive episode [179]. Anxiety symptoms will be assessed via the General Anxiety Disorder-7 (GAD-7) [180], a brief instrument used in primary care settings that has been validated in numerous menopause cohorts [181-183]. Sleep quality and disturbances will be assessed via the Pittsburgh Sleep Quality Index (PSQI), a self-report questionnaire that assesses sleep quality over a one-month interval that has shown strong reliability and validity in non-clinical samples [184]. Additionally, the PSQI is regularly used in middle-aged Australian cohorts [185, 186]. The Menopause-Specific Quality of Life (MENQOL) questionnaire will be used to measure changes in quality of life [187]. The MENQOL has four domains (vasomotor, physical, psychosocial, and sexual) and has been used extensively in clinical and epidemiological research over two decades [188].

# Potential Risks

Potential side effects of TMS include seizure induction; transient acute hypomania induction; syncope; transient headache, local pain, neck pain, toothache, paraesthesia; transient hearing changes; and burns from scalp electrodes [67]. Side effects are rare and TMS is considered a safe and tolerable intervention when participants are appropriately screened [75]. To minimise the risk of adverse events, individuals who have contraindications to TMS will be identified using the Transcranial Magnetic Stimulation Adult Safety Screen questionnaire during the screening phase and will be excluded from the study.

The electrical activity in the brain will be measured through EEG. EEG is non-invasive, with minimal discomfort involved. The fitting of the electrode cap to participants’ heads may be associated with a small amount of discomfort. Discomfort will be minimised by ensuring that the cap is the correct size, and the researcher will continually check in with the participants throughout the cap fitting process to ensure that the cap remains comfortable.

Participants may feel discomfort during sample collection. Participants will be assured that their biospecimens will be collected by a researcher who is suitably qualified in Good Clinical Practice, venepuncture, and first aid and follows the current best practice. Participants may feel apprehensive during the blood sample collection and will be assured that all needles used are sterile, single-use, and disposable, hence the risk of skin infection or blood-borne virus transmission is minimal. As with routine blood tests, participants may feel faint during or after the sample collection, and may experience bleeding, bruising, or soreness at the site of collection. Participants will be advised that these risks are minimal and will be required to remain for observation for 15-minutes post blood draw if they experienced faintness. Participants will be encouraged to seek medical treatment if necessary.

Regarding sample analysis, participants may feel apprehensive about the intended use of their samples. Participants will be assured that analysis will be targeted towards a group of related metabolites which have been biochemically annotated and characterised. The investigator will store the samples in a secure storage space with adequate measures to protect confidentiality.

Appropriate social distancing will be maintained where possible, and PPE will be provided and worn to reduce the likelihood of the transmission of viruses. There are no additional risks.

Some participants may share experiences or information which may be negative or distressing (for example, mental or cognitive status, medical history). We will advise the participant to let us know if any of the questions asked trigger a response which causes distress. Distressed participants will be advised to contact HealthDirect on 1800 022 222, as suggested by the Australian Menopause Society. We will also advise distressed participants to seek assistance that day from their general practitioner.

# Adverse Event Reporting

In terms of adverse event reporting, the investigator team will refer to the following definitions:

* An adverse event (AE) is defined as any medical event affecting the clinical trial participant. An AE may include any unfavourable and unintended sign, symptom, new disease, or exacerbated disease associated with the use of the intervention, whether considered related to the intervention. Each AE will be evaluated for severity, causality, and expectedness, and may be reclassified as a serious event based on the circumstances.
* An adverse reaction (AR) is defined as an AE that has been attributed to the intervention in terms of causality.
* A serious adverse event (SAE) is defined as an event that occurs which: (a) results in death; (b) is life threatening; (c) requires hospitalisation or prolongation of existing hospitalisation; (d) results in persistent or significant disability or incapacity; (e) is a congenital anomaly or birth defect; and/or (f) is considered serious by the investigator.
* A serious adverse reaction (SAR) is defined as a SAE which is causally related to the intervention.
* A suspected unexpected serious adverse reaction (SUSAR) is any SAE which has not been previously reported for the intervention and is suspected to be related to the intervention.

The investigator will monitor each participant for AEs during the study, and all AEs reported will be recorded in the Case Report Form (CRF). AEs will be collected and recorded from the first day of the study intervention until the end of the follow-up period at the timepoints specified in Figure 1. All AEs will be reported to the WSU HREC via the Annual Report to assist with monitoring of the project. All SAEs will be recorded and reported to the WSU HREC immediately upon becoming aware of the event (within 24 hours).

After an initial adverse event or severe adverse event (SAE) report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up. Follow up information for an SAE should be reported to the Sponsor.

# Statistical Considerations

A data-driven approach will be applied to de-identified data in StataTM (StataCorp, Texas, USA). Normality checks will be performed for all variables via visual inspection of histograms prior to statistical analyses to determine whether parametric or non-parametric approaches should be used. To compare participant baseline characteristics, two-tailed independent group *t*-tests with equal variances assumed will be used for all continuous variables, and chi-squared tests will be conducted for categorical variables. Dependent variables (e.g., cognitive and psychological test scores) taken at baseline and all following timepoints (endpoint and follow-up) will be analysed for within-subject and between-subject (active vs. sham) comparisons using generalised linear modes with planned simple contrasts for the within-subjects factor of time. To determine the relationship between biomarkers and changes in cognition and mood, a logistic regression analysis will be performed.

A possible signal of efficacy will be explored via effect-size estimates of changes tertiary outcomes (cognition and mood). Effect sizes, means, SDs, and CIs will be reported. Normality checks will be performed, and data will be transformed if necessary. Where appropriate, parametric tests will be applied. A generalised linear model with fixed and random effects will be applied for the tertiary outcomes. Variables will include the between-subjects factor of group (active vs. sham) and within-subjects factor of time (baseline, endpoint, follow-up). Pearson correlation coefficients (or their non-parametric counterpart) or multivariate regression involving tertiary outcomes will be conducted. All tests will be carried out one-tailed and using an alpha level of 0.05.

# Project Significance

Up to 67 % of females experiencing the menopause transition are affected by cognitive deficits, including subjective cognitive complaints. Approximately 47 % of women experience mood symptoms, including depressed mood and anxiety. There are no available treatments to effectively manage these debilitating symptoms, and the underlying mechanisms are not well understood, despite majorly impacting quality of life and daily activities. The lack of treatments available for managing the cognitive and psychological symptom profile, coupled with a limited understanding of the underlying mechanisms driving the changes, warrants the need for research into novel treatment options. This pilot clinical trial will address this evidence-practice gap by using non-invasive brain stimulation to improve cognition and mood in females going through the late menopause transition through a pilot clinical trial. Findings have the potential to advance our understanding of the underlying mechanisms that affect cognition and mood in menopause and offer the potential for new non-invasive treatments to mitigate symptoms. Findings from this research may improve the experience of the 80,000 Australian women who move into the menopause transition each year and mitigate the financial impacts of untreated menopause symptoms on the workforce.

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