Neuropsychiatric Disease and Treatment

Dovepress
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LETTER

Reassessing the Role of Mind-Regulating Acupuncture in Post-Stroke Depression: Promising but Not Yet Definitive [Letter]

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Dear editor

We commend Xie et al for performing a randomized controlled trial (RCT) to evaluate the clinical efficacy of Mind-Regulating Acupuncture (MRA) in post-stroke depression (PSD) and their hypothesis that its antidepressive effects may involve the modulation of the microbiota-gut-brain axis.[1] While this study contributes to the evidence base for acupuncture in PSD, several methodological limitations, likely influenced by real-world constraints such as limited resources and sample size, merit critical discussion.

Alignment Between Trial Design and the Stated Research Objectives

Xie et al state that their objective was to evaluate MRA's efficacy in PSD, yet their parallel-group RCT compared (1) Venlafaxine combined with routine post-stroke rehabilitation (pharmacotherapy plus motor, speech, and cognitive training) versus (2) the same regimen with added MRA.[1] While this additive design is clinically relevant for assessing MRA as an adjunct therapy in real-world practice, it precludes conclusions regarding whether MRA has independent antidepressive properties. Therefore, despite reflecting typical clinical scenarios, the design constrains the ability to delineate the specific effects attributable to MRA alone.

Furthermore, the absence of a placebo/sham-acupuncture control prevents determination of whether the symptom improvement [ie, reductions in the 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$) scores] stem from physiological effects of acupuncture or placebo responses.

We acknowledge that withholding antidepressants from both groups would raise ethical concerns. However, incorporating a sham-acupuncture control (eg, Streitberger needles[2]) could help isolate specific treatment effects, albeit with recognition of the ongoing debate regarding its validity and limitations.[3] Alternatively, we recommend that the authors clarify their rationale for the selected comparison group to better contextualize the combined or synergistic effects under investigation.

Potential Overestimation of Acupuncture's Therapeutic Role

The conclusion that "MRA effectively treats PSD"[1] is unsupported by the study design, which at best suggests that MRA may augment Venlafaxine's antidepressive effects. However, it remains unclear whether this enhancement is attributable to specific or non-specific effects of acupuncture.

Received: 5 August 2025
Accepted: 6 August 2025
Published: 12 August 2025

Xie et al also reported that MRA significantly improved neurological function and daily living abilities, as measured by changes in NIH Stroke Scale and Barthel Index scores.[1] MRA was primarily described as a mental state regulation technique. However, the Barthel Index assesses functions such as feeding, bathing, dressing, grooming, and bowel/bladder control,[4] covers areas not clearly linked to psychological intervention. Therefore, the observed improvements are more likely the result of the conventional rehabilitation provided to both groups. That said, MRA might have exerted indirect effects by alleviating depression-related apathy and enhancing motivation for daily activities—though this hypothesis requires further validation. Currently, without additional controls or mediation analyses, attributing these functional improvements primarily to MRA risks overinterpreting its therapeutic contribution.

Insufficient Detail on Intervention Delivery

Xie et al describe using a semi-standardized intervention combining a fixed set of core acupoints with additional acupoints based on TCM syndrome patterns.[1] The core acupoints listed were Baihui (GV20), Yintang (EX-HN3), Shenmen (HT7), Neiguan (PC6), and Taichong (LR3). However, their discussion section mentions Baihui (GV20), Shenting (GV24), and Shuigou (GV26) as used acupoints,[1] while Shenting (GV24) and Shuigou (GV26) were absent from the methods section. It is therefore unclear whether these acupoints were used or, if used, what needling techniques were applied, thus limiting the study's reproducibility.

Additionally, the "Acupoint Selection" section lists three TCM syndromes—*Liver-Qi* stagnation, *Heart-Spleen* deficiency, and *Phlegm-Qi* stagnation—and additional acupoints for each, yet fails to specify needling techniques for these supplementary acupoints.[1] According to the STRICTA checklist, detailed description of acupuncture techniques at each acupoint is essential.[5]

Finally, the authors emphasize that routine post-stroke rehabilitation was "personalized" for each of the 92 recruited patients regardless of group allocation.[1] This introduces significant variability, complicating result interpretation and raising concerns about the comparability of groups.

Ambiguities in Inclusion/Exclusion Criteria and TCM Pattern Classification

The authors enrolled PSD patients classified into three TCM syndrome patterns but did not justify why only these three were selected or whether they represent all PSD presentations.[1] Our review of *Acupuncture* and *TCM Internal Medicine* textbooks and guidelines found no clear or widely accepted evidence supporting this specific three-pattern taxonomy. Even assuming these patterns are valid, subgroup analyses stratified by TCM pattern are necessary to assess whether certain PSD subtypes respond differently to MRA as an adjunct to Venlafaxine. Such analyses would help clinicians identify which subtype patients are more likely to benefit. However, the authors did not conduct these analyses.

Furthermore, inclusion criteria required depression (HAM-D_{17} scores $\geq$17) and stroke diagnosis, but no method distinguished depression onset before or after stroke.[1] Thus, patients with pre-existing depression may have been misclassified as PSD. Despite excluding patients with a psychiatric history, underdiagnosed pre-stroke depression could still be included, given the high rate of depression underdiagnosis in clinical practice (8.5% to over 50%).[6]

Insufficient Clarity and Completeness in Outcome Assessment

Although the flow diagram indicates follow-up, only pre- and post-treatment data are reported.[1] The follow-up duration and outcomes assessed during this period are unclear.

PSD is commonly associated with cognitive impairment.[7] Studies demonstrate that stroke patients with major depression have lower Mini-Mental State Examination scores than matched non-depressed stroke patients.[7,8] It is unclear whether cognitive impairment affected patients' ability to complete outcome measures independently or with assistance, and whether assessments were self- or proxy-reported.

Lastly, safety outcomes are not reported,[1] leaving adverse events and their management unknown. The safety profile of MRA combined with conventional post-stroke treatment, including its potential to mitigate Venlafaxine-related adverse reactions, remains unknown.

The "Microbiota-Gut-Brain Axis" Speculation Lacks Mechanistic Evidence and Involves Logical Leaps

Xie et al attempt to attribute MRA's antidepressive effect to modulation of the microbiota-gut-brain axis.[1] Although their mechanistic interpretation is suggestive and the authors maintain a cautious, exploratory tone—acknowledging correlations rather than causation and calling for additional causal studies like fecal microbiota transplantation—it still lacks sufficient experimental support and cannot justify stronger inferences.

The microbiota-gut-brain axis is a complex bidirectional signaling network involving gut microbiota and metabolites [eg, short-chain fatty acids (SCFAs), indole derivatives from tryptophan metabolism, branched chain amino acids, and peptidoglycans], microbial components (eg, lipopolysaccharides), as well as neural circuits including the vagus nerve and the enteric nervous system.[9–11] To establish MRA's effects via this axis, the following evidence would be required: (1) demonstrable shifts in microbial composition; (2) quantifiable changes in microbial metabolites; (3) alterations in neurochemical markers (eg, neurotransmitters, neurotrophic factors); (4) indices of mood improvement; and (5) significant statistical associations among these variables.

In Xie et al's study, only a single stool sample was collected after eight weeks of acupuncture treatment,[1] precluding assessment of whether microbial changes were induced by MRA or pre-existing. Moreover, the microbiota analysis was limited to partial genus-level shifts, without linear discriminant analysis effect size (LEfSe) or false discovery rate correction, and key mediators such as SCFAs,[12] lipopolysaccharides,[11] or tryptophan metabolites[13] were not measured. Although serum serotonin and brain-derived neurotrophic factor (BDNF) levels were reported, their correlations with microbial changes and HAM-D_{17} score reduction were not examined.

A major confounding factor is Venlafaxine administration to all participants, as this drug independently alters gut microbiota,[14] neurotransmitter levels,[15] and BDNF expression.[16] Without controlling for these pharmacological effects, the attribution of observed changes to MRA alone is unwarranted.

Taken together, while the current findings are suggestive, they remain insufficient to substantiate a causal link between MRA and PSD improvement via the microbiota-gut-brain axis.

Conclusion and Recommendations

In summary, although Xie et al investigated MRA's therapeutic effects and mechanisms in PSD through an exploratory lens, their study highlights areas for methodological refinement in design, execution, and reporting. Particularly, while the proposed microbiota-gut-brain axis mechanism is thoughtfully hedged as correlative, it lacks sufficient biological evidence for stronger causal inferences.

Future studies should: (1) optimize control groups to disentangle the effects of antidepressants and acupuncture; (2) provide detailed intervention and outcome assessment protocols; (3) conduct medium-to-long-term follow-up including safety evaluations to fully judge the role and value of MRA as an independent treatment or an adjunct to standard care in PSD; and (4) incorporate additional mechanistic biomarkers (eg, SCFAs, tryptophan metabolites) with systematic correlation or pathway analyses.

We appreciate the authors' efforts and look forward to more rigorous acupuncture research providing robust evidence for PSD treatment.

Abbreviations

BDNF, Brain-Derived Neurotrophic Factor; HAM-D_{17}, 17-item Hamilton Depression Rating Scale; LEfSe, Linear Discriminant Analysis Effect Size; MRA, Mind-Regulating Acupuncture; PSD, Post-Stroke Depression; RCT, Randomized Controlled Trial; SCFAs, Short-Chain Fatty Acids; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture.

Author Contributions

Fei-Yi Zhao: Conceptualization, Investigation, Formal analysis, Writing – original draft. Yuen-Shan Ho: Conceptualization, Methodology, Formal analysis, Writing – review & editing. Qiang-Qiang Fu: Formal analysis, Writing – review & editing. All

authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding was received.

Disclosure

The authors declare no competing interests in this communication.

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