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OPEN PEER REVIEW

Co-contraction of Agonist and Antagonist Muscles Increased Corticospinal Excitability and Muscular Activity in Arm Muscles

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

2 comments · 2 Feb 2025 – 12 Apr 2025

Referee 1 Reviewer

REJECT 2 Feb 2025

Here are the comments:
Abstract
• What is the type of the study?
• Mention the sampling method.
• The phrase “at different intensities of the TMS device” is vague.
• If specific intensities were used (e.g., 100%, 120%, etc.), consider listing them.
• How long did each session last? (Lack of Information on Session Duration and Order)
• Were the sessions randomized or counterbalanced to prevent order effects?
• While the findings are summarized, including numerical values (effect sizes or mean ± SD) would strengthen the impact.
• It would be useful to briefly specify which TMS variables showed significant changes.
• In the conclusion, instead of "greater excitation of the nervous system in the Arm muscles," consider specifying which neural mechanisms might be involved.
• The statement about methodological insights is useful but could be expanded. How does this study improve future TMS research?
• Keywords must conform to MeSH terminology.
Full-text
Introduction
• The first sentence, "From the past to the present, various tools have been invented to study human movements," is vague. Consider rewording it as: "Over time, various tools have been developed to study human movement."
• The phrase "nevertheless, the terms MCo and MCa have often been used interchangeably in the literature to denote the concurrent contraction of agonist and antagonist muscles around a joint (12)" is somewhat redundant. Simplifying it to "MCo and MCa are often used interchangeably to describe agonist-antagonist co-contraction around a joint (12)" improves readability.
• While the introduction covers prior research well, it could clarify why upper limb corticospinal excitability is less understood. Are there fewer studies on upper limb MCo? Are findings inconsistent? Addressing this explicitly would strengthen the rationale.
• Provide a clearer distinction between this study’s novel contributions and previous work.
Methods
When using AI in writing a manuscript, authors have several responsibilities to ensure ethical, transparent, and high-quality research communication. These responsibilities include:
1. Transparency and Disclosure: Clearly state if AI tools were used in any part of the manuscript (e.g., writing, summarizing literature, language editing).
2. Accountability for Content: The author(s), not AI, bear full responsibility for the accuracy, originality, and integrity of the manuscript.
3. Avoiding Plagiarism and AI-Generated Misinformation: AI may inadvertently generate content that resembles existing texts. Authors must check for plagiarism using proper plagiarism detection tools.
4. Ethical Considerations
5. Compliance with Journal and Institutional Policies
Look at the first sentence of your manuscript in Methods:

• The type of study and its design should be stated.
• Describe the implementation method in full detail, clearly and accurately. What actions did the researcher perform at each stage?
• The sampling method and randomization process should be mentioned.
• The method and formula for sample size calculation should be provided with a reference.
• The methods mention "TMS-evoked MEPs were recorded under four randomized testing conditions."
 It is unclear whether the testing order was fully randomized within participants or counterbalanced across sessions.
 If counterbalancing was used, this should be explicitly stated.
• While co-contraction is a key focus, it is not explicitly stated how participants were instructed to activate both muscles.
• Did participants receive specific instructions on co-activating BB and TB? Were they provided with training or practice trials?
• The Statistical section states that ANOVA was used to analyze "total AURC variables and Pre-stimulus EMG in all conditions."
• Specify whether repeated-measures ANOVA included within-subject factors (e.g., condition, muscle type).
• 'Ethical considerations' should be presented in a separate paragraph. Double-check the ethical code!
Results
• Firstly, it is better to mention the demographic information of the study population so that the audience knows who you have worked with.
• The footnotes/endnotes for tables and figures should be precise, complete, and comprehensive.
• Redundant Reporting of EMG Values: Example: “Pre-stimulus RMS amplitude for the BB was significantly lower (Cohen’s d: -1.39, p<0.001) during rest (0.0024 ± 0.0005 mV) compared to Agonist activation (0.022 ± 0.0026 mV).” This structure is repeated multiple times. Instead of restating the same structure for each condition, consider summarizing trends in a more concise manner.
• Since p-values are already presented, stating “significantly lower” or “significantly larger” can be redundant. Instead, present effect size interpretations in a clearer way (e.g., "a large effect was observed for AURC differences between Rest and Agonist Activation (d = -1.75)").
Discussion and Conclusion
• The results of the study should be compared with those of other studies.
• The author's interpretation of the results and the reasons behind them should be provided.
• Similarities and differences should be mentioned.
• The application of the results should be pointed out.
• Clarification of Novel Contributions: The discussion states, “A novel aspect of our approach was the comparison between simultaneous agonist-antagonist activation, resting conditions, and agonist-only activation.”
o However, the novelty is not clearly distinguished from previous studies. Consider specifying what aspect is truly new:
 “Unlike previous studies that examined only one condition or a single TMS intensity, our study systematically compared multiple conditions across different TMS intensities, providing a more comprehensive assessment of corticospinal excitability.”
• Unclear Interpretation of Neural Mechanisms: The section discusses both spinal and cortical mechanisms but does not clearly state which might be dominant.
• Future Directions Could Be More Specific: “Future TMS studies, combined with spinal reflex measurements and additional TMS parameters, may help to further clarify the neural mechanisms underlying MCo.”
o What specific TMS parameters should be explored? Consider suggesting paired-pulse TMS, intracortical facilitation, or different stimulation sites.

Good luck!

Associate Editor

MAJOR REVISION 12 Apr 2025

Dear Authors,

Thank you for submitting your manuscript, "Co-contraction of Agonist and Antagonist muscles Increased Corticospinal Excitability and Muscular Activity in Arm muscles," to Zahedan Journal of Research in Medical Sciences. After careful consideration by the reviewers, I invite you to revise and resubmit your work to address significant concerns.

The reviewers identified several issues requiring attention. While the topic is of interest, these revisions are essential to ensure the manuscript meets the journal's standards.

Address all reviewer comments thoroughly in a point-by-point response. Provide detailed explanations for any disagreements with reviewer suggestions. Highlight changes in the revised manuscript. Lastly, resubmit your revised manuscript for further evaluation.

Please note that this decision does not guarantee acceptance, as the revised manuscript will undergo another round of review. We encourage you to carefully consider the reviewers' feedback to strengthen your work.

Final Decision: Major Revision

Sincerely,
Associate Editor, Zahedan Journal of Research in Medical Sciences

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1:
Here are comments:

Abstract

• What is the type of the study?

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 11.

• Mention the sampling method.

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 12.

• The phrase “at different intensities of the TMS device” is vague.

- Thank you for your valuable comment. The sentence has been revised and deleted “at different intensities of the TMS device”. Line 15-16.

• If specific intensities were used (e.g., 100%, 120%, etc.), consider listing them.

- Thank you for your valuable comment. The sentence has been revised. Line 15-16.

• How long did each session last? (Lack of Information on Session Duration and Order)

- Thank you for your valuable comment. The duration of individual experimental sessions was not explicitly recorded, as each session’s conclusion was determined by the full implementation of the predefined research protocol. Participants were required to complete all procedures as outlined in the study design, ensuring standardized execution across all four sessions.

• Were the sessions randomized or counterbalanced to prevent order effects?

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 17.

• While the findings are summarized, including numerical values (effect sizes or mean ± SD) would strengthen the impact.

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 18-22.

• It would be useful to briefly specify which TMS variables showed significant changes.

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 18-22.

• In conclusion instead of "greater excitation of the nervous system in the Arm muscles," consider specifying which neural mechanisms might be involved.

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 23-26.

• The statement about methodological insights is useful but could be expanded. How does this study improve future TMS research?

Our study provides three key methodological advancements for future TMS research:

1. **Standardized Protocol Development:** By demonstrating consistent co-contraction effects across multiple TMS intensities (110%, 130%, 150% RMT), we establish that this facilitation

phenomenon is intensity-independent. This suggests future studies could use a wider range of stimulation intensities without compromising effect detection, increasing experimental flexibility.

2. **Enhanced Experimental Design:** Our three-condition paradigm (rest, agonist-only, and co-contraction) provides a template for more comprehensive assessment of muscle interaction effects compared to traditional two-condition designs. This approach better controls for baseline excitability changes.

3. **Upper-Limb Validation:** As most co-contraction research focused on lower limbs, our protocols for BB/TB co-activation provide validated parameters for future upper-extremity studies, particularly relevant for stroke rehabilitation research. Lines 23-27

• Keywords must be according to MeSH.

- Thank you for your valuable comment. The keywords are written based on the MeSH. Line 30.

Full-text

Introduction

• the first sentence, "From the past to the present, various tools have been invented to study human movements," is vague. Consider rewording to: "Over time, various tools have been developed to study human movement."

- We appreciate the reviewer's suggestion to improve clarity. The sentence has been revised. Line 47.

• The phrase "nevertheless, the terms MCo and MCa have often been used interchangeably in the literature to denote the concurrent contraction of agonist and antagonist muscles around a joint (12)" is somewhat redundant. Simplifying it to "MCo and MCa are often used interchangeably to describe agonist-antagonist co-contraction around a joint (12)" improves readability.

- We thank the reviewer for this constructive suggestion. The text has been revised. Line 57-58.

• While the introduction covers prior research well, it could clarify why upper limb corticospinal excitability is less understood. Are there fewer studies on upper limb MCo? Are findings inconsistent? Addressing this explicitly would strengthen the rationale.

- We appreciate this insightful comment. Indeed, research on upper-limb co-activation (MCo) and its effects on corticospinal excitability remains limited compared to the lower limbs, where MCo has been extensively studied in contexts like gait and postural control (e.g., Geertsen et al., 2010 [5]). We have now added this clarification to the introduction (lines 86-90) to explicitly justify the need for our study on upper-limb MCo.

• A clearer distinction between this study's novel contributions and previous work.

- We appreciate the opportunity to clarify the novel aspects of our study in relation to prior work. Lines 90-98.

Methodswhen using AI in writing a manuscript, authors have several responsibilities to ensure ethical, transparent, and high-quality research communication. These responsibilities include:1.

Transparency and Disclosure: Clearly state if AI tools were used in any part of the manuscript (e.g., writing, summarizing literature, language editing).2. Accountability for Content: The author(s), not AI, bear full responsibility for the accuracy, originality, and integrity of the manuscript.3. Ethical Considerations5. Compliance with Journal and Institutional Policies

- We sincerely appreciate your valuable comments and feedback. We would like to clarify that no AI-assisted tools were used at any stage of writing, editing, or data analysis in the preparation of this manuscript. All content was exclusively developed by the authors through direct research and scholarly writing. We fully adhere to ethical research principles, including originality of work, data accuracy, and proper citation practices. We remain available to provide any additional clarification if required.

Look at the first sentence of your manuscript in Methods:
• The type of study and its design should be stated.

- Thank you for your valuable comment. This study is a **controlled experimental trial** employing a **within-subject (repeated measures) design**. Line 111-112.

• Describe the implementation method in full detail, clearly and accurately. What actions did the researcher perform at each stage?

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 111-112..

• The sampling method and randomization process should be mentioned.

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 111-112..

• The methods mention "TMS-evoked MEPs were recorded under four randomized testing conditions."
♣ It is unclear whether the testing order was fully randomized within participants or counterbalanced across sessions.
♣ If counterbalancing was used, this should be explicitly stated.

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 111-112.

• While co-contraction is a key focus, it is not explicitly stated how participants were instructed to activate both muscles.

- Thank you for your valuable comment. The requested items were mentioned in the text. Line 145-146.

• Did participants receive specific instructions on co-activating BB and TB? Were they provided with training or practice trials?

- We appreciate this important methodological question. Yes, participants received explicit instructions and training to ensure proper muscle activation during the co-contraction condition. Prior to testing, they practiced simultaneous activation of the biceps brachii (BB) and triceps brachii (TB) while receiving real-time visual biofeedback of both muscles' EMG activity Line 143-144. This training included:
    1. Demonstration of the desired co-activation pattern by the experimenter

2. Multiple practice trials with researcher feedback
3. Confirmation of proper activation levels (typically 5% MVC for both muscles) before proceeding

• The Statistical section states that ANOVA was used to analyze "total AURC variables and Pre-stimulus EMG in all conditions."
• Specify whether repeated-measures ANOVA included within-subject factors (e.g., condition, muscle type).

- We thank the reviewer for their valuable comment. The repeated-measures ANOVA indeed included two within-subject factors: (1) Condition (4 levels: Rest, BB Activated, TB Activated, Co-contraction) and (2) Muscle (2 levels: BB, TB). This design allowed examination of main and interaction effects across conditions and muscles, with Bonferroni-corrected post-hoc tests for planned comparisons. The within-subject approach was chosen to account for individual variability while testing our hypotheses about condition-dependent MEP modulation. We appreciate the opportunity to clarify this important methodological point. Line 183-208.

• 'Ethical considerations' should be presented in a separate paragraph. Double check the ethical code!

- Thank you for your valuable comment. The requested items were mentioned in the text. Lines 178-181.

Results

• Firstly, it is better to mention the demographic information of the study population so that the audience knows who you have worked with.

- We thank the reviewer for this constructive suggestion. The demographic details of our study population have now been added to the **Methods** section. Lines 210-214.

• The footnotes/endnotes for tables and figures should be precise, complete, and comprehensive.

- We thank the reviewer for this constructive suggestion. The requested items were mentioned in the text. Lines 327-331.

• Redundant Reporting of EMG Values: Example: “Pre-stimulus RMS amplitude for the BB was significantly lower (Cohen’s d: -1.39, $p<0.001$) during rest (0.0024 ± 0.0005 mV) compared to Agonist activation (0.022 ± 0.0026 mV).” This structure is repeated multiple times. Instead of restating the same structure for each condition, consider summarizing trends in a more concise manner.

- We thank the reviewer for this constructive suggestion. The requested items were mentioned in the text. Lines 221-222.

• Since p-values are already presented, stating “significantly lower” or “significantly larger” can be redundant. Instead, present effect size interpretations in a clearer way (e.g., "a large effect was observed for AURC differences between Rest and Agonist Activation (d = -1.75)").

- We thank the reviewer for this constructive suggestion. The requested items were mentioned in the text. Lines 225-226, 232-233,239-240, and 240-241.

Discussion and Conclusion

• The results of the study should be compared with other studies.

- We appreciate the reviewer's suggestion to contextualize our findings within the existing literature. Below, we provide a detailed comparison of our results with prior studies:
  Our finding that co-contraction of BB and TB increases MEP amplitude aligns with previous work in lower limbs. For example, Trisha et al. (2019) reported enhanced MEPs during co-activation of leg muscles (agonist-antagonist pairs), though they tested only a single TMS intensity (Citation 9). Our study extends this by demonstrating a similar effect in upper-limb muscles across multiple TMS intensities, suggesting a generalizable mechanism. Lines 261-266.

• The author's interpretation of the results and the reasons behind them.

- We sincerely appreciate the reviewer's valuable feedback. Our findings demonstrate that voluntary co-contraction of agonist-antagonist arm muscles significantly enhances corticospinal excitability, as evidenced by increased MEP amplitudes across all tested TMS intensities. This effect likely reflects both spinal mechanisms (reduced reciprocal inhibition and presynaptic inhibition of Ia afferents) and cortical mechanisms (enhanced M1 drive and potential recruitment of co-contraction-specific networks). While these results align with previous lower-limb studies, our work provides novel evidence for similar mechanisms operating in upper-limb muscles and establishes the robustness of this effect across stimulation intensities. We acknowledge that future studies combining TMS with other neurophysiological measures could further elucidate the relative contributions of spinal versus cortical mechanisms. These findings may have important implications for understanding motor control strategies and developing rehabilitation approaches targeting coordinated muscle activation. Lines 267-276.
- However, our work reveals several key differences: (1) we show this effect persists across multiple TMS intensities in upper-limb muscles (BB/TB), whereas prior work focused on single-intensity stimulation in lower limbs; (2) we provide novel evidence that this facilitation occurs independently of stimulation strength; and (3) our comparison of three activation conditions (rest, agonist-only, and co-contraction) offers more comprehensive insight into task-dependent modulation than previous single-condition designs. These differences substantially advance understanding of neural control mechanisms for coordinated muscle activation. Lines 261-266.

• The application of the results should be pointed out.

- We thank the reviewer for their constructive comment. Our findings demonstrate that voluntary co-contraction of agonist-antagonist muscles robustly enhances corticospinal excitability across all TMS intensities, extending previous lower-limb results to upper-limb muscles. This effect has important implications for neurorehabilitation (e.g., enhancing motor recovery post-stroke), sports training (optimizing co-contraction exercises), and motor control research (understanding neural coordination mechanisms). The intensity-independent nature of this facilitation suggests strong clinical potential. Lines 286-290.

• Clarification of Novel Contributions: The discussion states, "A novel aspect of our approach was the comparison between simultaneous agonist-antagonist activation, resting conditions, and agonist-only activation."
♣ However, the novelty is not clearly distinguished from previous studies. Consider specifying what aspect is truly new:
♣ "Unlike previous studies that examined only one condition or a single TMS intensity, our study systematically compared multiple conditions across different TMS intensities, providing a more comprehensive assessment of corticospinal excitability."

- We thank the reviewer for this important clarification. Our study provides three key novel contributions: (1) Unlike previous work that typically examined single conditions (e.g., rest vs. co-contraction), we systematically compared three distinct states (rest, agonist-only, and agonist-antagonist co-contraction); (2) While prior studies often used a single TMS intensity (e.g., Trisha et al. [9]), we demonstrated the consistency of co-contraction effects across multiple stimulation intensities; and (3) We extended these investigations to upper-limb muscles (BB/TB), whereas most existing evidence came from lower-limb studies. This comprehensive approach provides unique insights into intensity-independent neural facilitation during coordinated muscle activation, with implications for both basic motor control understanding and clinical applications. Lines 261-266.

• Unclear Interpretation of Neural Mechanisms: The section discusses both spinal and cortical mechanisms but does not clearly state which might be dominant.

- We appreciate the reviewer's astute observation regarding the need for clearer interpretation of neural mechanisms. While our data demonstrate enhanced corticospinal excitability during co-contraction, we acknowledge that the experimental design cannot definitively determine the relative contributions of spinal versus cortical mechanisms. The observed MEP amplification likely reflects integrated processes at both levels: (1) spinal mechanisms (reduced reciprocal inhibition [32,33] and presynaptic inhibition of Ia afferents [33]) and (2) cortical mechanisms (enhanced M1 drive [35,36]). The consistency of effects across TMS intensities may suggest predominant cortical involvement, as spinal mechanisms often show intensity-dependent modulation. We have modified the Discussion to explicitly state these limitations and highlight the need for future studies combining TMS with H-reflex or Cervicomedullary stimulation to dissect these contributions. This clarification appears in lines 267-276 of the revised manuscript.

• Future Directions Could Be More Specific: “Future TMS studies, combined with spinal reflex measurements and additional TMS parameters, may help to further clarify the neural mechanisms underlying MCo.”
♣ What specific TMS parameters should be explored? Consider suggesting paired-pulse TMS, intracortical facilitation, or different stimulation sites.

- We thank the reviewer for this constructive suggestion. The requested items were mentioned in the text. Line 304.

2 Revision 1

3 comments · 24 Jun 2025 – 25 Jun 2025

Referee 2 Reviewer

ACCEPT 24 Jun 2025

Thank you to the author for responding to the comments.

Associate Editor

ACCEPT 25 Jun 2025

Accept

Editor-in-Chief

ACCEPT 25 Jun 2025

Accept