The Journal of Physiology

Critical Considerations of the Contribution of the Corticomotoneuronal Pathway to Central Fatigue

Markus Amann, Simranjit K Sidhu, Chris J McNeil, and Simon C Gandevia
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The following individual(s) involved in review of this submission have agreed to reveal their identity: Jacob Thorstensen (Referee #2)

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Dear Professor Amann,

Re: JP-TR-2022-282564 "Critical considerations on the contribution of the corticospinal pathway to central fatigue" by Markus Amann, Simranjit K Sidhu, Chris J McNeil, and Simon C Gandevia

Thank you for submitting your Topical Review to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert referees and I am pleased to tell you that it is considered to be acceptable for publication following satisfactory revision.

The reports are copied at the end of this email. Please address all of the points and incorporate all requested revisions, or explain in your Response to Referees why a change has not been made.

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I hope you will find the comments helpful and have no difficulty in revising your manuscript within 4 weeks.

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I look forward to receiving your revised submission.

Yours sincerely,

Professor Laura Bennet
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EDITOR COMMENTS

I read with interest this review by Amann and colleagues, and the reports of the two expert reviewers. The review considers mechanisms underlying the development of central fatigue in the corticomotoneuronal pathway of muscles involved in

fatiguing exercise.

Two distinct forms of modulation of central fatigue are touched upon: i) endogenous modulation via effects of serotonin release on alpha motoneurons, and ii) exogenous modulation of cerebral cortex via transcranial direct current stimulation. The rationale for focussing on these two areas could be made clearer and strengthened. Why focus on serotonin and not other monoamines (dopamine, noradrenaline) that have been linked to central fatigue? Why focus on tDCS and not other forms of brain stimulation (e.g. rTMS, tACS)?

Both reviewers indicated that more methodological detail should be provided for key studies, so the reader can better understand key findings highlighted in the review and the context in which they apply.

As pointed out by reviewer 1, the summary section should be revised. In addition to the point raised by reviewer 1, the summary does not mention major themes of the review such as the modulation of central fatigue via serotonin and tDCS.

As pointed out by reviewer 2 a clear distinction should be made between endogenous and exogenous forms of neuromodulation.

Senior Editor:

Thank you for your review. We invite you to revise, and in particular address concerns about adding depth to some areas to ensure the readers know the methods, pros and cons and to more strongly address the challenges and future directions.

Please keep in mind The Journal's guidelines on Topical Reviews. "Topical Reviews should provide a succinct and accessible synthesis of current information in rapidly-developing areas of physiology. Authors should be forward-looking and present new questions for future research/developments and are encouraged to express their own opinion on a subject area and may be controversial if they wish to be, as science often moves fastest when ideas are challenged. However, Topical Reviews should still present a balanced view of the topic."

REFEREE COMMENTS

Referee #1:

This Topical Review aims to summarize our current understanding of corticospinal activity during exercise, mechanisms underlying the development of central fatigue, and the potential for brain stimulation to enhance motor cortical excitability and performance. Overall, I enjoyed reading this review as it was focussed and clearly written by an experienced team. I am confident that this review will be well received and will be of great interest to any researcher striving to understand how fatigue affects the corticospinal pathway and muscle activation.

Major comment

Throughout the review there were many instances where I found myself having to refer to original articles to understand some of the statements that were made. In many instances there were only brief descriptions (or no descriptions) of experiment protocols from the original articles. While I appreciate that the authors want to keep the content concise, I was challenged in several sections to understand which muscles were being described and what contraction tasks were being performed. Are MEPs or corticospinal excitability consistent for all muscles? Where are MEPs being measured from during locomotor tasks? Is it even possible to perform robust paired-pulse TMS studies to examine fatiguing contractions? Is the cortical end of the corticospinal pathway affected by neuromodulation? This should not be taken as a major criticism, but merely something that the authors may wish to consider. Slightly more detail to describe the original experiments would be very beneficial for the reader.

Specific comments.

Pg 5 third para. I had to read the sentence starting, "To decipher changes..." several times. The sentence finishes with "respectively" but I couldn't identify what the CMS, CMEP, and Mmax were respective of.

Pg 8 first para. I found myself wanting to know more about group III/IV afferents (and other afferents in general). With the authors expertise in sensory inputs to the motor system, I was curious to read the authors opinion regarding how sensory inputs affect cortical modulation. After all, afferents play a significant role in the circuit outlined in Figure 1.

Pg 11 second para. The authors may want to revisit the sentence, "as the effects are absent when the motoneurones are driven by antidromic stimulation..." Thorstensen found that antidromic activation is affected by 5-HT blockade without causing any changes to CMEPs. The latter finding still supports the authors statement that voluntary activation is required to detect neuromodulatory effects in the spinal cord.

Pg 14 second para. I didn't really see this as a set of summary statements. Because many of the methods of the original articles were not included, highlighting replication and reproducibility of research findings seemed to come out of nowhere.

Referee #2:

Overall comments

When discussing 'neuromodulation' throughout text, I suggest that authors make a clear contrast between endogenous neuromodulation (i.e., serotonin and other neurochemicals released from neurons), and exogenous forms of neuromodulation (i.e., tDCS). Where possible, 'non-invasive brain stimulation' or 'tDCS' should replace 'neuromodulation' to describe stimulation techniques that induce plastic effects in the brain. I acknowledge that neuromodulation is a broad term, and that both endogenous and exogenous forms of neuromodulation change the intrinsic properties of neurons within the motor cortex and spinal cord, but the physiology of tDCS and serotonergic drive to the spinal cord are markedly different, and this is an important distinction to make for a topical review in JPhysiol.

In this topical review, the use of 'corticospinal pathway' is described as encompassing both corticospinal neurons and spinal motoneurons. Perhaps, 'corticospinal-motoneuronal system/pathway' is more intuitive, so that when corticospinal is mentioned in text the reader is readily aware that the authors are discussing corticospinal cells and not the combined corticospinal-motoneuronal system and associated synapses.

Key points

Key point #3: 'Recent studies have highlighted changes in volitionally-induced neuromodulation of serotonergic effects at the motoneurone level.' Perhaps the authors would consider changing the wording of this key point. 'volitionally-induced neuromodulation of serotonergic effects' is not clear, as serotonin does the neuromodulation and is not itself neuromodulated, which is what this key point indicates.

Evaluating the excitability of the corticospinal pathway

This might be a picky comment, but CMEPs are conventionally referred to as 'cervicomedullary motor evoked potentials' and not 'cervicomedullary evoked potentials'.

The authors indicate that 'the CMEP lacks conventional presynaptic inhibition'. I understand the premise behind this statement, but electrophysiological responses are not technically inhibited but the neurons that generate these responses are inhibited. Do the authors mean 'corticospinal neurons recruited into the CMEP lack conventional presynaptic inhibition'?

Motor cortex excitability and fatigue

The authors indicate that: 'For example, MEP size increases as a percentage of Mmax with most sustained tasks (e.g., (Taylor et al., 1999) (Note: motoneuronal excitability is reduced and so cannot enhance MEP size).' It is important to indicate in text if a sustained task is maximal or submaximal, as this has important implications for recruitment and discharge of motoneurons.

'Specifically, MEP normalized to Mmax was reported to increase for an upper-limb muscle (Otieno et al., 2019), but remained unchanged for a lower-limb muscle (Gruet et al., 2014)'. Again, there needs to be some consideration of contraction intensity for the above statement, as differences in MEP behaviour have been observed even within the same muscle across different contraction intensities. E.g., for the biceps brachii during a sustained isometric submaximal elbow flexion fatigue task, MEPs tend to increase with fatigue when evoked during submaximal contraction but stay relatively consistent when evoked during brief MVCs that are intermittently performed throughout the submaximal contraction (see MEPs in Søgaard et al., 2006 and Thorstensen et al., 2020, both in JPhysiol).

More to the above, is this simply a lower versus upper limb argument? Or is there more to consider here? Do smaller hand muscles have more corticospinal input than big lower-limb extensors involved in postural control and locomotion (i.e., with a strong reticulospinal contribution)? What is the monosynaptic component of the MEP for hand muscles versus the quadriceps?

'During exhaustive cycling, it is reported in most studies that the MEP, when normalized to Mmax, remains unchanged'. More detail about the above studies is needed for readers, and for interpretation of underlying physiology. Were MEPs obtained from remote muscle not engaged in locomotion? Or muscles engaged during locomotion? Were MEPs elicited during different stages of locomotion? These are all sources of heterogeneity and need to be considered when making overarching claims about MEPs during locomotor tasks.

'In the future, experimental or technological advances are required to probe the functional relevance of fatigue-related changes in the MEP and SP.' Can the authors elaborate on this? What emerging technologies are important? I feel that this statement leaves the reader hanging, and I think the authors would be in a good position to tell the JPhysiol readership what they believe the next set of experiments could involve.

Motoneurones and fatigue

'These recent insights are important for the quantification of voluntary activation via TMS as compared to peripheral nerve stimulation. Specifically, these limits mean that voluntary activation assessed by peripheral nerve stimulation can be well below 100%, while voluntary activation assessed by TMS may appear complete.' I do not entirely follow the relevance for this part of text, especially how it relates to serotonin and motoneuron excitability. Are the authors indicating that serotonin will affect TMS measures of voluntary activation, but not twitch interpolation assessed with motor point stimulation? More clarity is needed.

Figure 3 (I found this figure difficult to follow)

Were the MEPs obtained in resting muscle? This is not clear from the figure legend.

For panel B, were the MEPs obtained pre- or post-fatigue, or during the fatigue task? This is not clear from the figure legend

and is essential for interpretation of this panel.

MEPs in panel B were not normalised to Mmax but were normalised in panel D (but were then normalised to a control condition). This makes it difficult to understand what percentage of the motoneuron pool was recruited by TMS, and whether this contributes to some of the heterogeneity between results. The authors might want to consider including this information if possible.

For panel D, it is unknown what muscle the MEPs were recorded from. This information needs to be included.

For panel D, error bars are included in the figure, but these are not defined in the figure legend. Figures should be stand alone.

REQUIRED ITEMS:

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END OF COMMENTS

Confidential Review **07-Sep-2022**

EDITOR COMMENTS

I read with interest this review by Amann and colleagues, and the reports of the two expert reviewers. The review considers mechanisms underlying the development of central fatigue in the corticomotoneuronal pathway of muscles involved in fatiguing exercise.

Two distinct forms of modulation of central fatigue are touched upon: i) endogenous modulation via effects of serotonin release on alpha motoneurons, and ii) exogenous modulation of cerebral cortex via transcranial direct current stimulation. The rationale for focussing on these two areas could be made clearer and strengthened. Why focus on serotonin and not other monoamines (dopamine, noradrenaline) that have been linked to central fatigue? Why focus on tDCS and not other forms of brain stimulation (e.g. rTMS, tACS)?

RESPONSE:

To address your point, we now introduce the idea of endogenous vs exogenous modulation early in the paper and continue to remind the reader of this difference throughout the paper. There is not a real rationale for focusing on serotonin and tDCS, we simply chose these areas because of the considerable amount of previous work allowing for a (somewhat) clear message. We deliberately refrained from other areas to avoid speculation and chose examples with a clear message. This 'rationale' has now been added to the Introduction.

Both reviewers indicated that more methodological detail should be provided for key studies, so the reader can better understand key findings highlighted in the review and the context in which they apply.

RESPONSE:

Agreed. We have now revised the manuscript and include more details on the studies we discuss.

As pointed out by reviewer 1, the summary section should be revised. In addition to the point raised by reviewer 1, the summary does not mention major themes of the review such as the modulation of central fatigue via serotonin and tDCS.

RESPONSE:

We have now changed the summary to address the point raised by reviewer 1. We also included statements related to serotonin and tDCS.

As pointed out by reviewer 2 a clear distinction should be made between endogenous and exogenous forms of neuromodulation.

RESPONSE:

We have now revised the manuscript and clearly distinguish between endogenous and exogenous forms of neuromodulation throughout the paper.

Senior Editor:

Thank you for your review. We invite you to revise, and in particular address concerns about adding depth to some areas to ensure the readers know the methods, pros and cons and to more strongly address the challenges and future directions.

RESPONSE:

By thoroughly revising the manuscript and responding to all of the reviewers' comments, we have significantly changed the paper to address these issue.

REFEREE COMMENTS

Referee #1:

This Topical Review aims to summarize our current understanding of corticospinal activity during exercise, mechanisms underlying the development of central fatigue, and the potential for brain stimulation to enhance motor cortical excitability and performance. Overall, I enjoyed reading this review as it was focussed and clearly written by an experienced team. I am confident that this review will be well received and will be of great interest to any researcher striving to understand how fatigue affects the corticospinal pathway and muscle activation.

RESPONSE:

Thank you for your suggestions. We have now responded to your comments and revised the manuscript accordingly.

Major comment

Throughout the review there were many instances where I found myself having to refer to original articles to understand some of the statements that were made. In many instances there were only brief descriptions (or no descriptions) of experiment protocols from the original articles. While I appreciate that the authors want to keep the content concise, I was challenged in several sections to understand which muscles were being described and what contraction tasks were being performed. Are MEPs or corticospinal excitability consistent for all muscles? Where are MEPs being measured from during locomotor tasks? Is it even possible to perform robust paired-pulse TMS studies to examine fatiguing contractions? Is the cortical end of the corticospinal pathway affected by neuromodulation? This should not be taken as a major criticism, but merely something that the authors may wish to consider. Slightly more detail to describe the original experiments would be very beneficial for the reader.

RESPONSE:

We agree with your points. Therefore, throughout the article, we have now added experimental details, including the contraction intensity (submaximal vs. maximal) of the fatiguing protocol, and the muscle from which the EMG responses were recorded. In answer to your question about paired-pulse TMS studies to examine fatiguing contractions, yes, it is entirely possible to conduct robust studies. Owing to the word limit for the article, we very concisely summarized the paired-pulse literature, and provided only a small number of citations. However, dozens of studies have been conducted during the last two decades. The uncertainty of the effect of fatigue on short-interval, paired-pulse MEPs is most likely due to the disparate methodological approaches; e.g., MEP recordings during contraction vs. relaxation, isometric vs. dynamic fatiguing tasks, different approaches to setting stimulator intensities, etc.

Specific comments.

Pg 5 third para. I had to read the sentence starting, "To decipher changes..." several times. The sentence finishes with "respectively" but I couldn't identify what the CMS, CMEP, and Mmax were respective of.

RESPONSE:

We have now revised the sentence and hope our edits improve readability of this statement.

Pg 8 first para. I found myself wanting to know more about group III/IV afferents (and other afferents in general). With the authors expertise in sensory inputs to the motor system, I was curious to read the authors opinion regarding how sensory inputs affect cortical modulation. After all, afferents play a significant role in the circuit outlined in Figure 1.

RESPONSE:

We appreciate your comment and have therefore revised the manuscript to offer more details on the role of group III/IV muscle afferent feedback on the motor system. However, the dilemma we face is that a more involved discussion on the effects of these sensory neurons on the corticospinal-motoneuronal pathway would require substantially more space / words – especially when contrasting and comparing single joint vs locomotor exercise and the various methodologies used to manipulate group III/IV muscle afferents to investigate their effects. Given the restrictions associated with Topical Reviews, a more detailed debate is therefore unfortunately not possible without cutting back on other aspects of the manuscript, i.e. sections which also suffer from the word limitation. We do, however, refer the reader to a recently published review article solely focusing on the effects of muscle afferents on the central motor pathway during exercise.

Pg 11 second para. The authors may want to revisit the sentence, "as the effects are absent when the motoneurones are driven by antidromic stimulation..." Thorstensen found that antidromic activation is affected by 5-HT blockade without causing any changes to CMEPs. The latter finding still supports the authors statement that voluntary activation is required to detect neuromodulatory effects in the spinal cord.

RESPONSE:

Agreed, the statement was not very clear. We have revised the sentence to clarify the message. With this new version, we don't think it's crucial to mention the Thorstensen observation.

Pg 14 second para. I didn't really see this as a set of summary statements. Because many of the methods of the original articles were not included, highlighting replication and reproducibility of research findings seemed to come out of nowhere.

RESPONSE:

We now included, throughout the manuscript, additional details on the methods utilized in the original articles. However, we appreciate and agree with your point and have therefore removed this paragraph from the summary section and – as we think this is still an important point to raise – placed it at the end of the main part of the manuscript, i.e. before the Summary section

Referee #2:
Overall comments
When discussing 'neuromodulation' throughout text, I suggest that authors make a clear contrast between endogenous neuromodulation (i.e., serotonin and other neurochemicals released from neurons), and exogenous forms of neuromodulation (i.e., tDCS). Where possible, 'non-invasive brain stimulation' or 'tDCS' should replace 'neuromodulation' to describe stimulation techniques that induce plastic effects in the brain. I acknowledge that neuromodulation is a broad term, and that both endogenous and exogenous forms of neuromodulation change the intrinsic properties of neurons within the motor cortex and spinal cord, but the physiology of tDCS and serotonergic drive to the spinal cord are markedly different, and this is an important distinction to make for a topical review in JPhysiol.
RESPONSE:
Agreed. In response to your concern, we have now revised the entire manuscript to clarify the endogenous vs exogenous forms of neuromodulation and replaced ‘neuromodulation’ with ‘non-invasive brain stimulation’ where appropriate.

In this topical review, the use of 'corticospinal pathway' is described as encompassing both corticospinal neurons and spinal motoneurons. Perhaps, 'corticospinal-motoneuronal system/pathway' is more intuitive, so that when corticospinal is mentioned in text the reader is readily aware that the authors are discussing corticospinal cells and not the combined corticospinal-motoneuronal system and associated synapses.
RESPONSE:
We have faced this comment in the past and agree with you, ‘corticospinal-motoneuronal pathway’ is certainly clearer and actually more appropriate. We have therefore adjusted the manuscript and use ‘corticospinal-motoneuronal pathway’ or ‘corticomotoneuronal pathway’ throughout the paper.

Key points
Key point #3: 'Recent studies have highlighted changes in volitionally-induced neuromodulation of serotonergic effects at the motoneurone level.' Perhaps the authors would consider changing the wording of this key point. 'volitionally-induced neuromodulation of serotonergic effects' is not clear, as serotonin does the neuromodulation and is not itself neuromodulated, which is what this key point indicates.
RESPONSE:
Agreed. Based on your comment, we have completely revised the ‘Key Points’ to clarify this and other issues associated with the initial version.

Evaluating the excitability of the corticospinal pathway
This might be a picky comment, but CMEPs are conventionally referred to as 'cervicomedullary motor evoked potentials' and not 'cervicomedullary evoked potentials'.
RESPONSE:
Yes, agreed, thanks for pointing this out. We have now rectified this error.

The authors indicate that 'the CMEP lacks conventional presynaptic inhibition'. I understand the premise behind this statement, but electrophysiological responses are not technically inhibited but the neurons that generate these responses are inhibited. Do the authors mean 'corticospinal neurons recruited into the CMEP lack conventional presynaptic inhibition'?

RESPONSE:
Yes, that was our intended meaning. We have corrected the loose language.

Motor cortex excitability and fatigue
The authors indicate that: 'For example, MEP size increases as a percentage of Mmax with most sustained tasks (e.g., (Taylor et al., 1999) (Note: motoneuronal excitability is reduced and so cannot enhance MEP size).' It is important to indicate in text if a sustained task is maximal or submaximal, as this has important implications for recruitment and discharge of motoneurons.
RESPONSE:
We have now modified the text to indicate that MEP size increases during submaximal- and maximal-intensity sustained isometric contractions.

'Specifically, MEP normalized to Mmax was reported to increase for an upper-limb muscle (Otieno et al., 2019), but remained unchanged for a lower-limb muscle (Gruet et al., 2014)'. Again, there needs to be some consideration of contraction intensity for the above statement, as differences in MEP behaviour have been observed even within the same muscle across different contraction intensities. E.g., for the biceps brachii during a sustained isometric submaximal elbow flexion fatigue task, MEPs tend to increase with fatigue when evoked during submaximal contraction but stay relatively consistent when evoked during brief MVCs that are intermittently performed throughout the submaximal contraction (see MEPs in Søgaard et al., 2006 and Thorstensen et al., 2020, both in JPhysiol).
RESPONSE:
Again, we have added experimental details to indicate the intensity of contraction and the tested muscle. Further, we have replaced both the Otieno and Gruet references so that the cited studies used the same basic task (repeated MVCs).

More to the above, is this simply a lower versus upper limb argument? Or is there more to consider here? Do smaller hand muscles have more corticospinal input than big lower-limb extensors involved in postural control and locomotion (i.e., with a strong reticulospinal contribution)? What is the monosynaptic component of the MEP for hand muscles versus the quadriceps?
RESPONSE:
It was not our intention to put forth a specific argument based on the location of the muscle or any other possible difference between muscles (e.g., the relative contribution of the corticospinal input) as we do not believe that there are sufficient data to draw such a conclusion. Instead, we simply provided two examples to convey concisely our main point; i.e., the response of the MEP to fatiguing isometric contractions is unpredictable. To avoid an implication of a known upper vs. lower limb disparity, we now refer to two studies conducted in the lower limb that have conflicting results.

'During exhaustive cycling, it is reported in most studies that the MEP, when normalized to Mmax, remains unchanged'. More detail about the above studies is needed for readers, and for interpretation of underlying physiology. Were MEPs obtained from remote muscle not engaged in locomotion? Or muscles engaged during locomotion? Were MEPs elicited during different stages of locomotion? These are all sources of heterogeneity and need to be considered when making overarching claims about MEPs during locomotor tasks.
RESPONSE:
In all cases, MEPs were recorded from leg muscles involved in the locomotor task; however, two of the cited studies recorded MEPs during an isometric contraction after the exhaustive cycling (Temesi et al., 2013; O'Leary et al., 2018) so we chose to omit these studies and focus on those that recorded MEPs during the fatiguing, locomotor task. Further, we made it clear that the data were collected from

the quadriceps muscles when they were actively contracting. Of note, we applied the same approach for the SP data.

'In the future, experimental or technological advances are required to probe the functional relevance of fatigue-related changes in the MEP and SP.' Can the authors elaborate on this? What emerging technologies are important? I feel that this statement leaves the reader hanging, and I think the authors would be in a good position to tell the JPhysiol readership what they believe the next set of experiments could involve.

RESPONSE:

This is tricky. Like the reviewer, we wish it were clear what technological advances would provide the information sought by those in this field of research. Unfortunately, we cannot foresee what these advances might be. We can, therefore, unfortunately not provide additional insight related to this point. We have modified the sentence to better reflect that we do not know what these advances could look like.

Motoneurones and fatigue

'These recent insights are important for the quantification of voluntary activation via TMS as compared to peripheral nerve stimulation. Specifically, these limits mean that voluntary activation assessed by peripheral nerve stimulation can be well below 100%, while voluntary activation assessed by TMS may appear complete.' I do not entirely follow the relevance for this part of text, especially how it relates to serotonin and motoneuron excitability. Are the authors indicating that serotonin will affect TMS measures of voluntary activation, but not twitch interpolation assessed with motor point stimulation? More clarity is needed.

RESPONSE:

Yes, that's exactly what we are indicating. We have now revised this part to more strongly emphasize the implication associated with 5-HT receptors on quantifying muscle activation via the use of TMS.

Figure 3 (I found this figure difficult to follow)

Were the MEPs obtained in resting muscle? This is not clear from the figure legend.

RESPONSE:

Apologies that this information was missed from the figure legend. The MEPs in panel B were measured during the task of 20% MVC, whereas the MEPs in panel D were measured in a resting muscle. This has now been clarified in the figure legend.

For panel B, were the MEPs obtained pre- or post-fatigue, or during the fatigue task? This is not clear from the figure legend and is essential for interpretation of this panel.

RESPONSE:

The MEPs were obtained during the task. This information has also been added in the figure legend.

MEPs in panel B were not normalised to Mmax but were normalised in panel D (but were then normalised to a control condition). This makes it difficult to understand what percentage of the motoneuron pool was recruited by TMS, and whether this contributes to some of the heterogeneity between results. The authors might want to consider including this information if possible.

RESPONSE:

Thank you for this comment. This occurrence is indeed one of the many factors that contribute to the heterogeneity between results. The study represented in panel B did not measure Mmax to account for muscle dependent changes which is a considerable limitation in the work. Whilst tDCS is not expected to influence the muscle, even subtle differences in the position of the electrodes on the muscle can

influence the measurement of the pool of motoneuron recruited by TMS. This has now been included in the manuscript.

For panel D, it is unknown what muscle the MEPs were recorded from. This information needs to be included.

RESPONSE:

We have now included that the MEPs were recorded from the hand muscle.

For panel D, error bars are included in the figure, but these are not defined in the figure legend. Figures should be stand alone.

RESPONSE:

We have now included that the MEPs are shown as mean ± SEM

Dear Professor Amann,

Re: JP-TR-2022-282564R1 "Critical Considerations of the Contribution of the Corticomotoneuronal Pathway to Central Fatigue" by Markus Amann, Simranjit K Sidhu, Chris J McNeil, and Simon C Gandevia

I am pleased to tell you that your Topical Review article has been accepted for publication in The Journal of Physiology, subject to any modifications to the text that may be required by the Journal Office to conform to House rules.

NEW POLICY: In order to improve the transparency of its peer review process The Journal of Physiology publishes online as supporting information the peer review history of all articles accepted for publication. Readers will have access to decision letters, including all Editors' comments and referee reports, for each version of the manuscript and any author responses to peer review comments. Referees can decide whether or not they wish to be named on the peer review history document.

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The accepted version of the manuscript will be published online, prior to copy editing in the Accepted Articles section.

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Yours sincerely,

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EDITOR COMMENTS

Reviewing Editor:

Two experts in the field have reviewed the revised manuscript. Both are of the opinion that it will be influential for researchers working on the mechanisms of central fatigue.

REFEREE COMMENTS

Referee #1:

The authors have satisfactorily addressed each of my comments. Importantly, the authors have significantly improved the clarity and readability of the manuscript. This is an excellent example of a focused Topical Review, which I am sure will be of great interest to researchers in the fatigue community.

Referee #2:

All my comments and concerns have been adequately addressed. I do not believe any more changes to the manuscript are required. I commend the authors on their topical review.

1st Confidential Review **20-Oct-2022**