

Mechanisms of Hebbian-like plasticity in the ventral premotor - primary motor network

Andrea Casarotto, Elisa Dolfini, Pasquale Cardellicchio, Luciano Fadiga, Alessandro D'Ausilio, and Giacomo Koch
DOI: 10.1113/JP283560

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The referees have opted to remain anonymous.

Review Timeline:

Submission Date:	04-Jul-2022
Editorial Decision:	01-Sep-2022
Revision Received:	29-Sep-2022
Accepted:	18-Oct-2022

Senior Editor: Katalin Toth

Reviewing Editor: Srikanth Ramaswamy

Transaction Report:

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Dear Professor Koch,

Re: JP-RP-2022-283560 "Mechanisms of Hebbian-like plasticity in the ventral premotor - primary motor network" by Andrea Casarotto, Elisa Dolfini, Pasquale Cardellicchio, Luciano Fadiga, Alessandro D'Ausilio, and Giacomo Koch

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-The most appropriate summary statistic (e.g. mean or median and standard deviation) must be used. Standard Error of the Mean (SEM) alone is not permitted.

-Exact p values must be stated. Authors must not use 'greater than' or 'less than'. Exact p values must be stated to three significant figures even when 'no statistical significance' is claimed.

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EDITOR COMMENTS

Reviewing Editor:

The manuscript in consideration by Casarotto et al. entitled 'Mechanisms of Hebbian-like plasticity in the ventral premotor - primary motor network' presents an interesting body of work on the effects of cortico-cortical paired associative stimulation (cc-PAS), a transcranial magnetic stimulation (TMS) protocol, on synaptic interactions between the ventral premotor cortex (PMv) and primary motor cortex (M1).

The authors used a battery of paired-pulse TMS protocols to probe the impact of PMv-M1 cc-PAS on human inhibitory neural networks as quantified by short and long intracortical inhibition protocols. The authors varied the direction of current stimulation in M1 to target different neuronal populations. The authors demonstrate that that PMv-M1 cc-PAS induces both LTP- or LTD-like in M1 neuronal activity that is strongly associated with bidirectional specific change in the I2-wave activity. The authors provide mechanistic insights on how PMv governs network activity in M1.

Overall, this is an influential piece of work. The manuscript is well-written, and the figures are clearly presented.

The reviewers have recommended revisions to the manuscript.

Senior Editor

The figures should depict SD instead of SEM.

REFEREE COMMENTS

Referee #1:

The manuscript titled 'Mechanisms of Hebbian-like plasticity in the ventral premotor - primary motor network' from Casarotto et.al presents a fascinating work about the effects of cc-PAS (cortico-cortical paired associative stimulation) on PMv-M1 circuits, critical for the organization of goal directed actions. To do so, they have used different paired-pulse TMS protocols to examine the impact of PMv-M1 cc-PAS on SICF (short intracortical facilitation protocol), on GABAergic circuits as measured by short (SICI) and long (LICI) intracortical inhibition protocols and finally, how the directionality of stimulation could affect the circuit. They show that the directionality of stimulations seems to induce two different long-lasting effect in M1, respectively identifiable as LTP and LTD as well as induce a specific modulation of the neuronal circuit responsible of the I2-wave, highlighting PMv as the specific source of the input to the primary motor cortex responsible for its generation.

Comments:

The manuscript has been written clearly and the different experimental conditions have been explained well to support their findings. The tabular representation of the experimental paradigms (Figure 1) was very useful and the discussion of the diverse measurements to study how the two areas are communicating with each other was highly interesting. A lot of effort and details have been provided in discussion as potential circuit mechanism behind the effects observed in the humans.

Major points:

1) Since several of the subjects obviously participated in more than one session, it would be critical to provide the following information: 1) how much time passed between each experiment 2) was there any difference between subjects who experienced multiple cc-PAS sessions vs those who only participated directly in that experiment 3) add these also to the figure 1 and table 1.

2) Since all the measurements MEP, SICI, LICI, SICF, ICF (experiment 1) were done to the same individual, they are not independent of each other. Please discuss if they could influence each other and how it was controlled.

3) Since the different ISI (experiment 2) were done in a randomized manner and not dependent on each other, line graph does not represent the data correctly as they are not showing an incremental relationship between the conditions. They should be analyzed with repeated measures two-way ANOVA: Different ISI (1.3, 2.1, 2.5, 3.3, 4.1 ms) vs time of measurement (pre, post).

4) Similar point as above for experiment 3.

Minor points:

1) Page 2, line 36: "...induces both LTP- or LTD-like in M1 neuronal activity" There should be something after LTD-like which is omitted. LTD-like aftereffects?

2) Page 2, line 38-39: PMv-M1 cc-PAS also induces a distinct modulation on LICI circuit and modulates PMv-M1 connectivity. Please rewrite this statement more clearly.

3) The bars in some graphs (Figure 2) were shifted. Adding individual data points to the bar graphs is recommended.

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The manuscript in consideration by Casarotto et al. entitled "The manuscript titled 'Mechanisms of Hebbian-like plasticity in the ventral premotor - primary motor network'" presents an interesting body of work on the effects of cortico-cortical paired associative stimulation (cc-PAS), a transcranial magnetic stimulation (TMS) protocol, on synaptic interactions between the ventral premotor cortex (PMv) and primary motor cortex (M1).

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Overall, this is an influential piece of work. The manuscript is well-written, and the figures are clearly presented. Specifically, I find that Figure 1 does a very good job in summarizing the various experimental protocols and interactions between PMv and M1.

I provide further comments below to improve the presentation of the manuscript.

1) Many parts in the manuscript appear a bit "jargony". For e.g. line 39 "PMv-M1 cc-PAS also induces a distinct modulation on LICI circuit and modulates PMv-M1 connectivity". Line 78 "In order to fill this gap, we investigated the modifications on PMv-78 M1 circuit and on M1 local circuitry after the PMv-M1 cc-PAS application". These lines could benefit from some rephrasing.

2) The experimental procedures could include some more detail. Because several measurements in experiment 1 (MEP, SICI, LICI, SICF, ICF etc.) were undertaken in the same subjects, it is not clear if lumping these numbers could skew the overall interpretation. This should be further clarified.

3) Although Figure 2 is already quite dense, it would be useful to show the individual data points across the measured indices to show the extent of the spread.

END OF COMMENTS

Confidential Review

04-Jul-2022

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- 2) Since all the measurements MEP, SICI, LICI, SICF, ICF (experiment 1) were done to the same individual, they are not independent of each other. Please discuss if they could influence each other and how it was controlled.
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I provide further comments below to improve the presentation of the manuscript.

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- 2) The experimental procedures could include some more detail. Because several measurements in experiment 1 (MEP, SICl, LICl, SICF, ICF etc.) were undertaken in the same subjects, it is not clear if lumping these numbers could skew the overall interpretation. This should be further clarified.
- 3) Although Figure 2 is already quite dense, it would be useful to show the individual data points across the measured indices to show the extent of the spread.

Dear Editor,

we are glad to receive these positive comments and suggestions. We revised our manuscript, following every point raised by the Reviewers and we modified the graphs, using SD and showing individual data points across the measured indices.

✓ EDITOR COMMENTS

- The figures should depict SD instead of SEM.
We depicted SD instead of SEM in all the figures.

✓ REQUIRED ITEMS FOR REVISION

- The contact information provided for the person responsible for 'Research Governance' at your institution is an author on this paper. Please provide an alternative contact who is not an author on this paper or confirm that the author whose email was provided has sole responsibility for research governance. This is the person who is responsible for regulations, principles and standards of good practice in research carried out at the institution, for instance the ethical treatment of animals, the keeping of proper experimental records or the reporting of results.
We confirm that Prof. Luciano Fadiga, Head of IIT@UniFe Center for Translational Neurophysiology (Istituto Italiano di Tecnologia), has sole responsibility for research governance.

1. Referee n.1

- Comments:
The manuscript has been written clearly and the different experimental conditions have been explained well to support their findings. The tabular representation of the experimental paradigms (Figure 1) was very useful and the discussion of the diverse measurements to study how the two areas are communicating with each other was highly interesting. A lot of effort and details have been provided in discussion as potential circuit mechanism behind the effects observed in the humans.
- Major points:
 1. Since several of the subjects obviously participated in more than one session, it would be critical to provide the following information: 1) how much time passed between each experiment 2) was there any difference between subjects who experienced multiple cc-PAS sessions vs those who only participated directly in that experiment 3) add these also to the figure 1 and table 1.
Thanks for this suggestion. Approximately two weeks elapsed between each experimental session. For this reason, we can safely exclude that subjects participating in more than one experimental session may present any difference with respect to those who took part in only one session. However, this point allowed us to add important information in the manuscript. We analyzed the MEPs registered from 13 subjects participating in one or more sessions. There was no significant difference between these groups ($t_{13} = 0.05$; $p = 0.96$). We integrated this information in the revision (page 12, lines 299-302).

2. Since all the measurements MEP, SICI, LICI, SICF, ICF (experiment 1) were done to the same individual, they are not independent of each other. Please discuss if they could influence each other and how it was controlled.

Thanks to this comment we had the opportunity to clarify also this point in the manuscript. Previous results (Ni et al. 2011) show that LICI protocol can influence the subsequent SICI acquisition, but LICI did not interact with a subsequent acquisition of ICF. Importantly, LICI was administered 100 ms before the SICI. In our first experiment, we randomized the presentation of each index thus cancelling out any potential order effect. At the same time, in our studies, each measurement was collected with an interval of 5 s, that should further cancel any carry over effect. We specified this point in method session (pages 9-10, lines 236-240)

Ni, Z., Gunraj, C., Wagle-Shukla, A., Udupa, K., Mazzella, F., Lozano, A. M., & Chen, R. (2011). Direct demonstration of inhibitory interactions between long interval intracortical inhibition and short interval intracortical inhibition. *The Journal of physiology*, 589(12), 2955-2962.

3. Since the different ISI (experiment 2) were done in a randomized manner and not dependent on each other, line graph does not represent the data correctly as they are not showing an incremental relationship between the conditions. They should be analyzed with repeated measures two-way ANOVA: Different ISI (1.3, 2.1, 2.5, 3.3, 4.1 ms) vs time of measurement (pre, post).

In the second experiment, we randomized the different ISI of the paired pulse stimulation, as they are independent measures. In order to represent in the best way, the specific pre-post modulation of each independent ISI, we modified the graph using a scatterplot. The statistical choice was informed by evidences that different I-waves derive from quite different synaptic structures. In particular, the I₁-wave arises from different presynaptic structures than the later I-waves. Later I-waves reflect activity from other cortical areas; while, the I₁-wave arises within M1 (Ziemann, 2020; Cattaneo et al., 2005; Shimazu et al., 2004). Due to the different origin of each I-wave, these should be considered separately and analyzed independently (see Cattaneo et al. 2005). The focus of the present experiments was to investigate the specific modulation of the I₂-wave after the cc-PAS protocol. A repeated measure ANOVA would instead be more suited to the investigation of the difference between different I-waves or between the I-waves and the baselines recorded at 2.1 and 3.3 ms intervals.

Cattaneo, L., Voss, M., Brochier, T., Prabhu, G., Wolpert, D. M., & Lemon, R. N. (2005). A cortico-cortical mechanism mediating object-driven grasp in humans. *Proceedings of the National Academy of Sciences*, 102(3), 898-903.

Shimazu, H., Maier, M. A., Cerri, G., Kirkwood, P. A., & Lemon, R. N. (2004). Macaque ventral premotor cortex exerts powerful facilitation of motor cortex outputs to upper limb motoneurons. *Journal of Neuroscience*, 24(5), 1200-1211.

Ziemann, U. (2020). I-waves in motor cortex revisited. *Experimental Brain Research*, 238(7), 1601-1610.

4. Similar point as above for experiment 3.

Thanks for the observation and the opportunity to clarify our statistical rationale. As for the previous experiment, our attention was focused on the pre/post effects and not on the interaction between the different intensities used for the conditioning stimulus.

This same approach matches with previous literature on the same topic (Hanajima et al., 2001; Mochizuki et al., 2004). In fact, the use of different intensities was aimed to target different PMv neural populations and for this reason we consider appropriate to treat the different PMv stimulation intensities separately.

Hanajima, R., Ugawa, Y., Machii, K., Mochizuki, H., Terao, Y., Enomoto, H., ... & Kanazawa, I. (2001). Interhemispheric facilitation of the hand motor area in humans. *The Journal of Physiology*, 531(Pt 3), 849.

Mochizuki, H., Huang, Y. Z., & Rothwell, J. C. (2004). Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. *The Journal of physiology*, 561(1), 331-338.

- Minor points.

1. Page 2, line 36: "...induces both LTP- or LTD-like in M1 neuronal activity" There should be something after LTD-like which is omitted. LTD-like aftereffects?

We have corrected the mistake: "... induces both LTP- or LTD-like aftereffect in M1 neuronal activity (page 3, lines 55).

2. Page 2, line 38-39: PMv-M1 cc-PAS also induces a distinct modulation on LICI circuit and modulates PMv-M1 connectivity. Please rewrite this statement more clearly.

We have modified this sentence in the manuscript (page 3, lines 57-58).

3. The bars in some graphs (Figure 2) were shifted. Adding individual data points to the bar graphs is recommended.

We apologize for the mistake, probably due to the file upload. We have followed the reviewer suggestion to correct and modify all the graphs adding (in the bar graphs) the individual points.

2. Referee n. 2:

- Points:

1. Many parts in the manuscript appear a bit "jargon". For e.g. line 39 "PMv-M1 cc-PAS also induces a distinct modulation on LICI circuit and modulates PMv-M1 connectivity". Line 78 "In order to fill this gap, we investigated the modifications on PMv-M1 circuit and on M1 local circuitry after the PMv-M1 cc-PAS application". These lines could benefit from some rephrasing.

Thanks to reviewer suggestion, we control and correct all the manuscript in order to improve the quality of it. In particular, we modify the two sentences highlighted in this first comment (page 3, lines 57-58; page 4, lines 97-99).

2. The experimental procedures could include some more detail. Because several measurements in experiment 1 (MEP, SICl, LICI, SICF, ICF etc.) were undertaken in the same subjects, it is not clear if lumping these numbers could skew the overall interpretation. This should be further clarified.

In the first experiment we randomized all measures, with 5 seconds of interval between each TMS pulse delivery, in order to avoid carry over effects. We clarified this point in the manuscript (pages 9-10, lines 236-240).

3. Although Figure 2 is already quite dense, it would be useful to show the individual data points across the measured indices to show the extent of the spread.

Following this useful suggestion, we modified every graph to make them clearer and effective. In particular, we added the individual data points across the recorded

indexes. Moreover, we have modified the graphs reporting the results of the second and third experiments according to the suggestions of Referee 1.

We would like to thank the reviewers for their helpful comments and we hope that the changes made to the article are in line with expectations. For any further comments we remain at your disposal.

Dear Dr Koch,

Re: JP-RP-2022-283560R1 "Mechanisms of Hebbian-like plasticity in the ventral premotor - primary motor network" by Andrea Casarotto, Elisa Dolfini, Pasquale Cardellicchio, Luciano Fadiga, Alessandro D'Ausilio, and Giacomo Koch

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EDITOR COMMENTS

The authors have addressed all concerns.

REFEREE COMMENTS

Referee #1:

Satisfied with the revisions.

Referee #2:

The authors have addressed all my concerns. I endorse the publication of the manuscript.

1st Confidential Review

29-Sep-2022
