Deepening the neurophysiological underpinnings of a visuo-motor *paired associative stimulation* (PAS) protocol through TMS-EEG coregistration

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1 – BACKGROUND

Hebbian associative plasticity has been implied in the formation of the association between sensory and motor representations of actions in the *action observation network* (AON)[1]. Recently, our research group developed a *paired associative stimulation* (PAS) protocol targeting the AON: the **mirror PAS** (m-PAS)[2,3].
The m-PAS repeatedly pairs transcranial magnetic stimulation (TMS) pulses over the right primary motor cortex (M1) with visual stimuli depicting abduction movements made with the index finger of the right hand (ipsilateral to TMS cortical site). The m-PAS **successfully induced new ipsilateral motor resonance responses, indexed by an atypical facilitation of cortico-spinal excitability during the observation of ipsilateral (right) hand movements** – i.e., conditioned during the protocol.

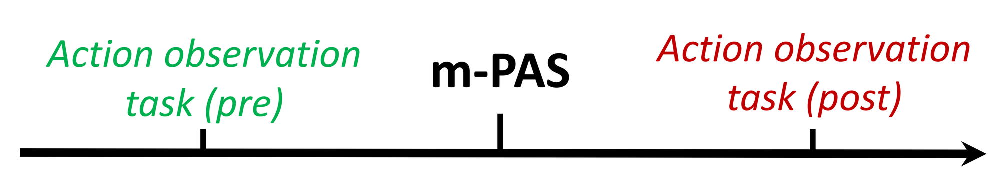
2 – AIMS

In the present study, we sought to deepen the **neurophysiological correlates of m-PAS-induced associative plasticity by exploiting TMS and electroencephalography coregistration (TMS-EEG)** to clarify the global cortico-cortical dynamics underlying the aftereffects of its administration.
During a standard action observation task depicting static/moving left-/right-hand index-finger movements, we simultaneously recorded **motor-evoked potentials** (MEPs) and **TMS-evoked potentials** (TEPs), before and after the administration of the m-PAS.

3 – METHODS and MATERIALS

3.1 Experimental procedure

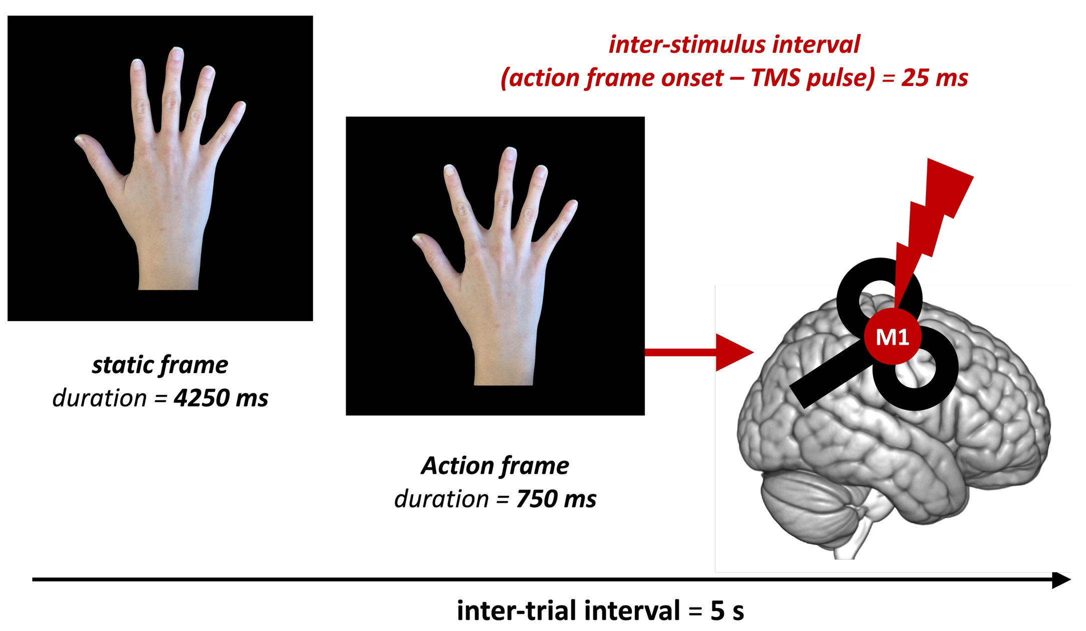
25 right-handed healthy participants tested (10 M)



Scan here for our previous works with the m-PAS!
Brain Stim 2020
Cortex 2023

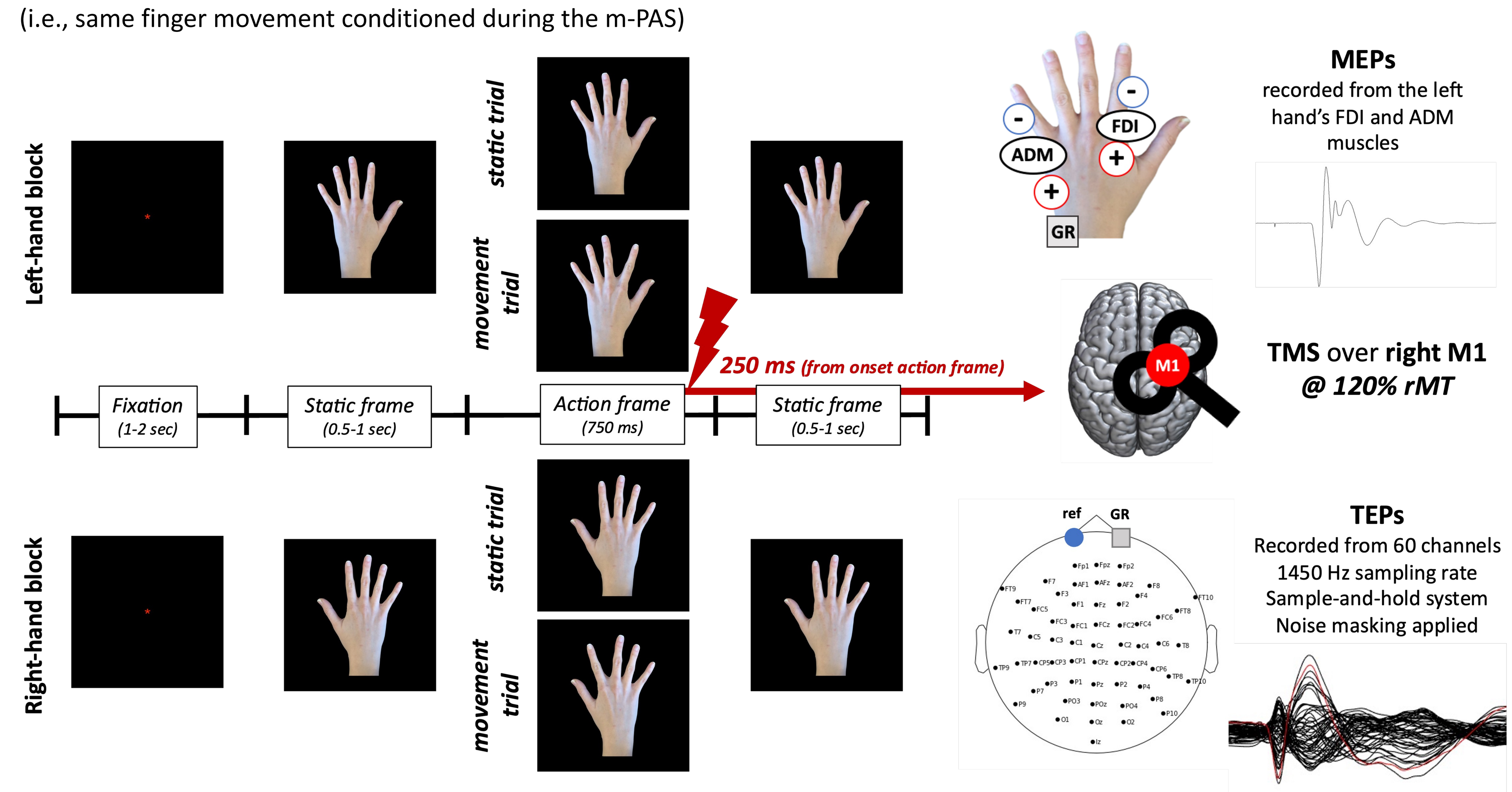
3.2 m-PAS [2,3]

- *Peripheral visual stimulus*: movement of the right-hand index finger
- *Cortical stimulus*: TMS pulse over right M1 @ 120% rMT
- 180 paired pulses @ 0.2 Hz (duration: 15 min)



3.3 Action observation task (MEP and TEP recording)

2 blocks of 160 trials each depicting left- (contralateral to TMS) or right-hand (ipsilateral to TMS) index-finger abduction movement (i.e., same finger movement conditioned during the m-PAS)



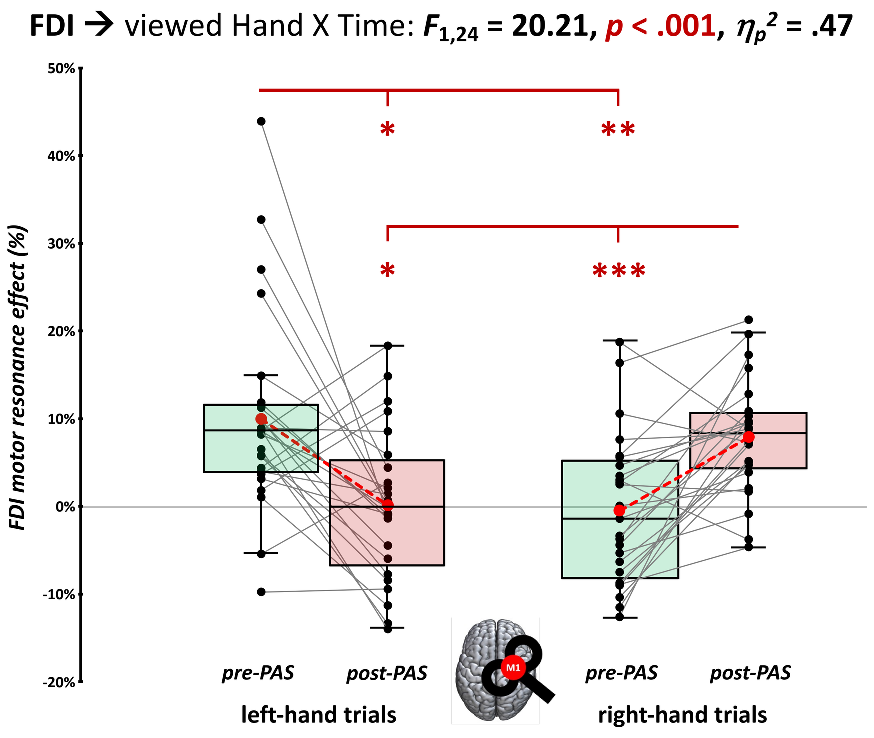
4 – RESULTS

* $p < .05$ ** $p < .01$ *** $p < .001$ *(Bonferroni corrected)*

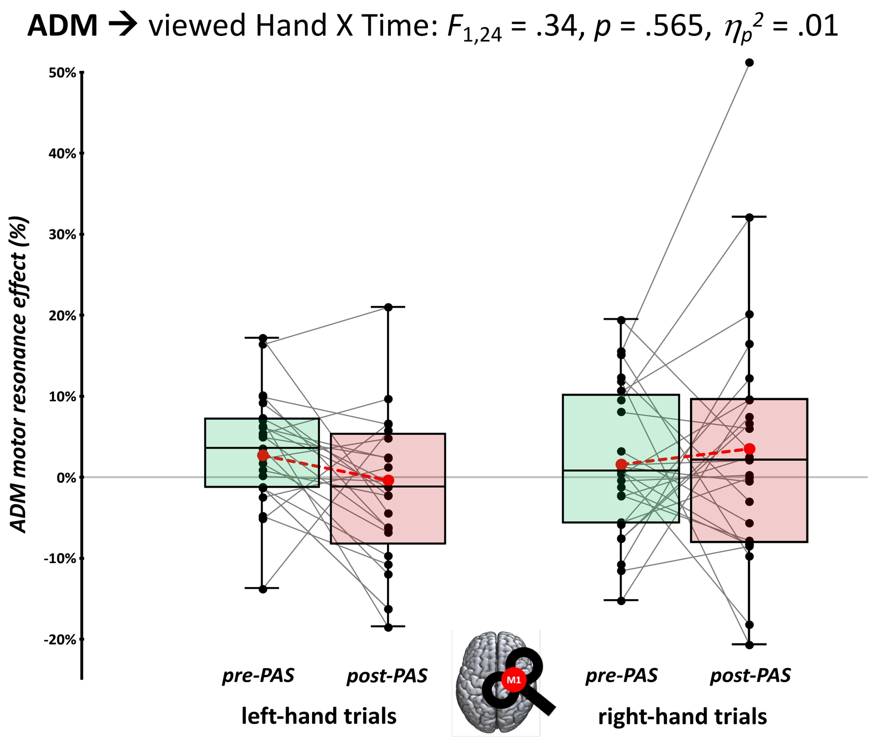
4.1 Motor Resonance

m-PAS effects on *'% motor resonance'* (ratio between MEPs amplitude in movement and static trials) were assessed through a 2 'Muscle' *(FDI, ADM)* X 2 'viewed Hand' *(left, right)* X 2 'Time' *(pre-PAS, post-PAS)* repeated measures ANOVA. A significant triple interaction was found (**$F_{1,24}$ = 9.8, p = .005, η_p^2 = .29**).

FDI → viewed Hand X Time: **$F_{1,24}$ = 20.21, $p < .001$, η_p^2 = .47**



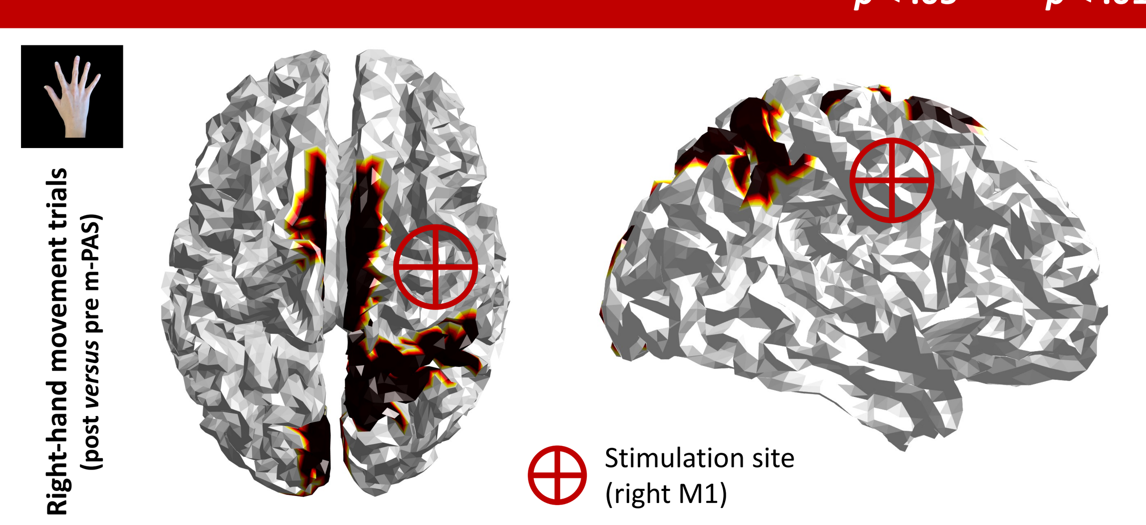
ADM → viewed Hand X Time: $F_{1,24}$ = .34, p = .565, η_p^2 = .01



4.2 Source analysis

TEP amplitude

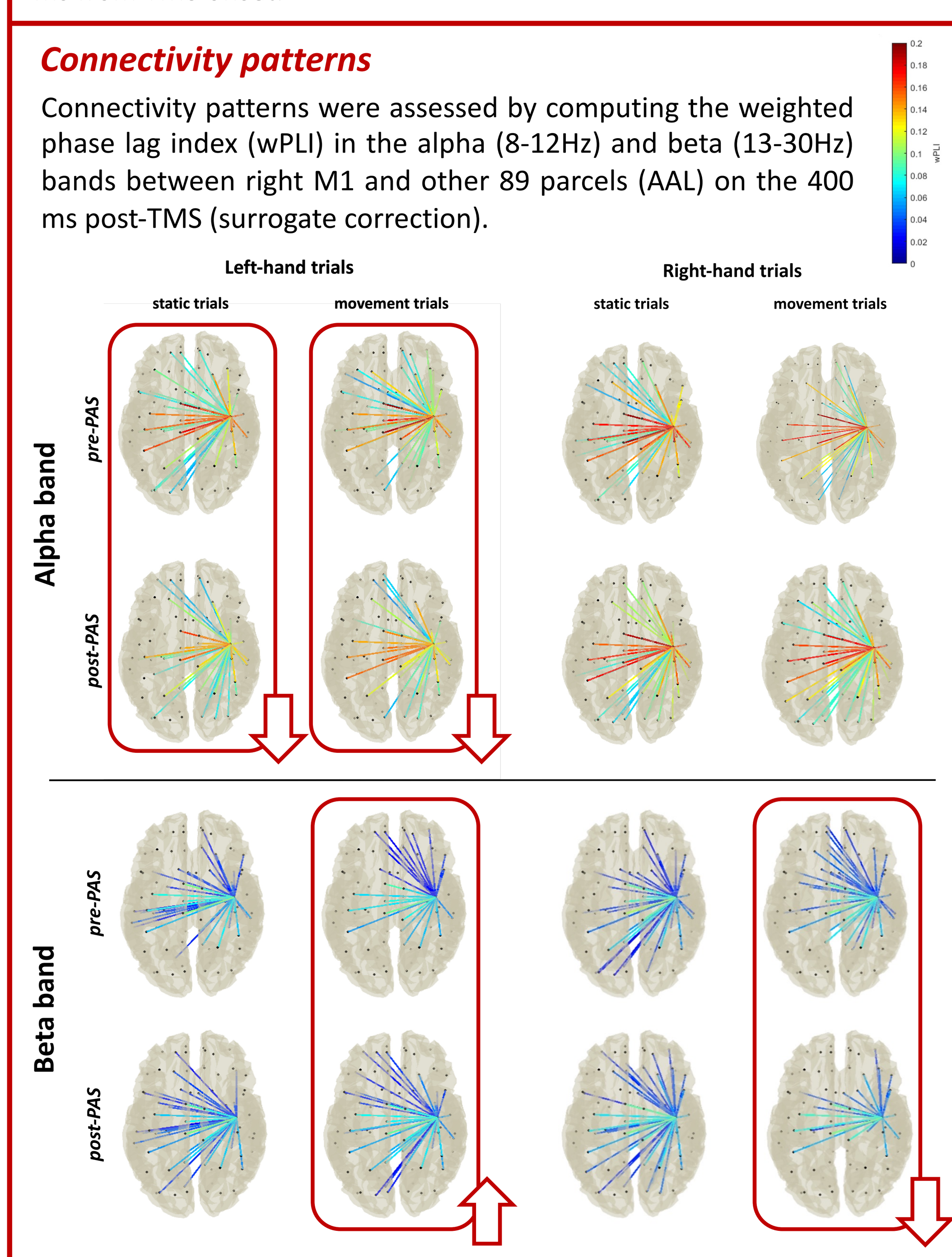
The effects of m-PAS on TEPs spatiotemporal profile were assessed at the sources level. Cluster-based t-test between post *versus* pre m-PAS TEPs were performed whole-brain for each AOT condition on the 0-300 ms post-TMS time window, p=.05, 10000 permutations.
We only found a significant positive cluster encompassing right-lateralized fronto-parietal regions (**p = .02**) during the observation of PAS-conditioned right-hand movement in a time window of 146-253 ms from TMS onset.



AAL parcel	Hemisphere
SMA	L/R
Middle cingulum	L/R
IPL	R
SPL	R
Paracentral lobule	R
Precuneus	R
Cuneus	L
Calcarine	L

Connectivity patterns

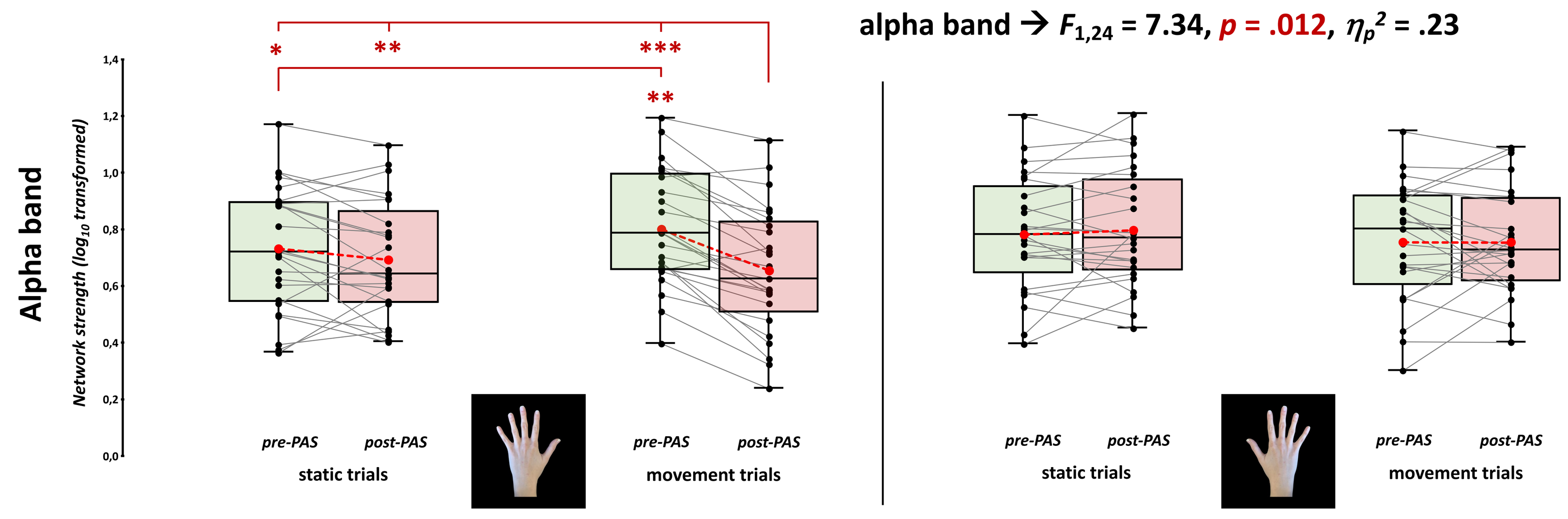
Connectivity patterns were assessed by computing the weighted phase lag index (wPLI) in the alpha (8-12Hz) and beta (13-30Hz) bands between right M1 and other 89 parcels (AAL) on the 400 ms post-TMS (surrogate correction).



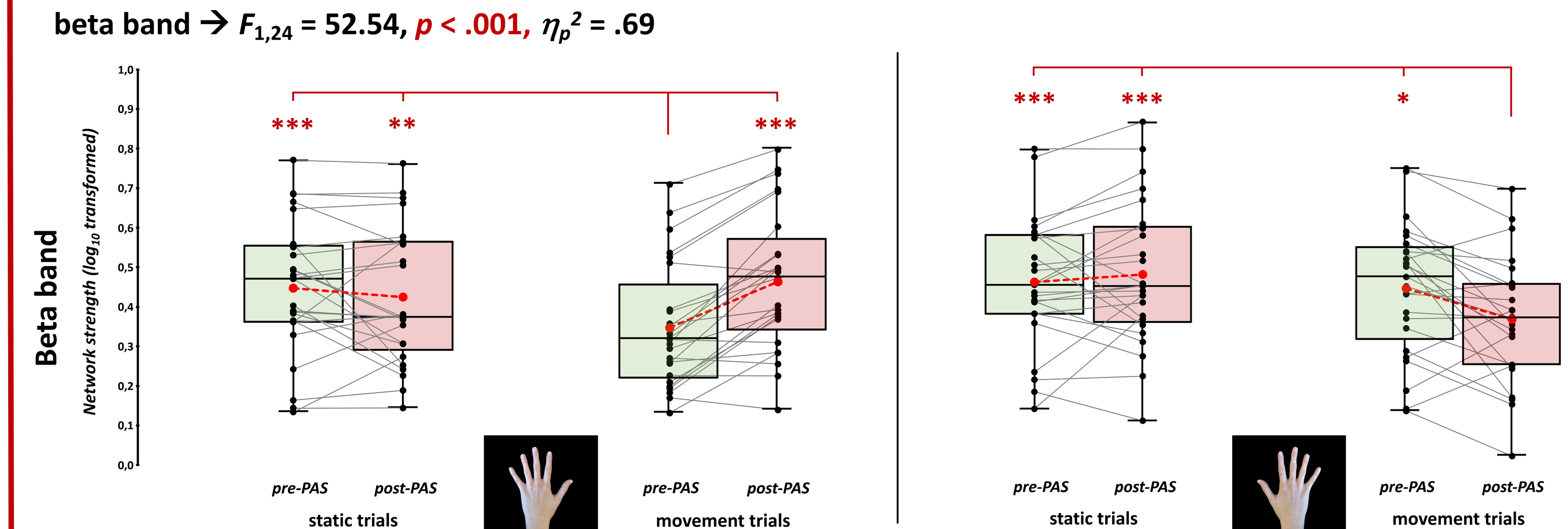
Connectivity strength

Connectivity strength was computed for each participant as the sum of all significant connections and compared with a 2 'viewed Hand' (*left, right*) x 2 'visual Stimulus' (*static, movement*) X 2 'Time' (*pre-PAS, post-PAS*) rm-ANOVA in alpha (8-12 Hz) and beta bands (13-30 Hz).

alpha band → **$F_{1,24}$ = 7.34, p = .012, η_p^2 = .23**



beta band → **$F_{1,24}$ = 52.54, $p < .001$, η_p^2 = .69**



5 – DISCUSSION and CONCLUSIONS

Motor resonance (MEPs) → as expected[2,3], **m-PAS induces the emergence of motor resonance for the conditioned** (right-hand movement) **visual stimulus**. At variance with previous studies, we also observed the **loss of motor resonance for the unconditioned** (left-hand) **movement**.

Effective connectivity → after m-PAS administration, selectively for the right-hand visual stimulus of movement and in a mid-late time window (150-250 ms), the **signal spread propagating from M1 increased toward a right lateralized cluster of cortical regions encompassing sensorimotor and parietal areas,** like SMA and the superior/inferior parietal lobules.

Functional connectivity → the **emergence of motor resonance** for PAS-conditioned right-hand stimuli is linked with **decreased beta connectivity between M1 and fronto-parietal regions** during the observation of right hand movements. The **loss of motor resonance** for left-hand stimuli are primarily linked with **decreased alpha** (for both trials type) **and increased beta connectivity** (specific for trials depicting movements).

Overall, our results provide evidence that **visuo-motor associative plasticity induced by the m-PAS could be tracked at a cortical level with TMS-EEG**. This highlights how the induction of novel motor resonance responses relies on the **reshape of complex cortical dynamics between key nodes of the AON.** This evidence suggests that cortico-cortical markers of motor resonance could be useful to extend the patterns found at corticospinal level.

6 – REFERENCES

1) Keysers, C., & Gazzola, V. (2014). Hebbian learning and predictive mirror neurons for actions, sensations and emotions. *Philosophical Transactions of the Royal Society B*, *369*, 20130175.
2) Guidali, G. et al. (2020). Paired Associative Stimulation drives the emergence of motor resonance. *Brain Stimulation*, 13, 627–636.
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