Modulating the response of the Primary Somatosensory cortex with a novel Paired Associative Stimulation protocol

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1 – BACKGROUND

An increasing number of evidence suggests the existence of a *Tactile Mirror System* in the human brain: **the same cortical network implicated in tactile perception**, which comprises the primary somatosensory cortex (S1), **also responds to the mere observation of tactile events.** It has been suggested that such cross-modal, mirror-like, responses of S1 may arise from Hebbian associative plasticity: the contingency of seeing a touch and the feeling of a tactile sensation on one's own body may reinforce synapses between visual and somatosensory neurons [1].

In this study we introduce a novel cross-modal Paired Associative Stimulation (cm-PAS) protocol [2]. In the cm-PAS, a visual stimulus depicting a hand being touched is repeatedly presented, paired with a Transcranial Magnetic Stimulation (TMS) pulse over S1.

2 – AIMS

In the **three experiments** of the study, our aim is to develop a novel PAS protocol targeting the *Tactile Mirror System* and to investigate the effects of induced plasticity:

- at a **behavioral** level, measuring tactile acuity with a 2-Point Discrimination Task (2-PDT);
- at a **neurophysiological** level, with the recording of Somatosensory Evoked Potentials (SEPs).

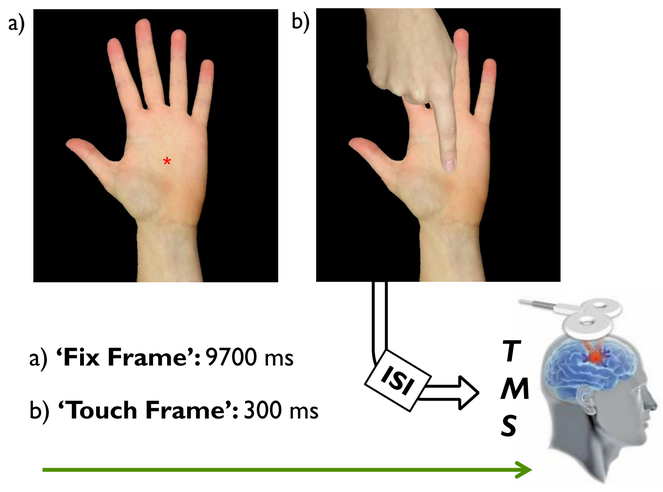
3 – METHODS and MATERIALS

cm-PAS *

* *adapted from standard S1 PAS protocol [3]*

- *Frequency:* 0.1 Hz
- *TMS intensity*: 150% resting Motor Threshold
- *Total trials*: 150
- *Total duration:* 25 minutes

- *cm-PAS visual stimuli (single-frame):*

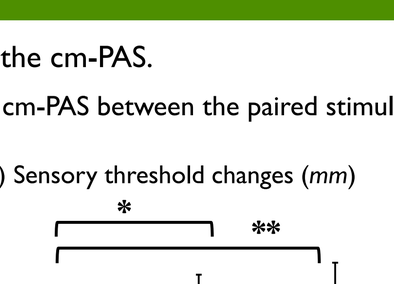


- *Tested PAS parameters:*

- *Experiment 1* → ISI between '*Touch frame*' onset and TMS pulse: 20 ms (*cm-PAS*$_{20}$) 60 ms (*cm-PAS*$_{60}$) and 100 ms (*cm-PAS*$_{100}$).

- *Experiment 2* → stimulated cortical area: right S1 (*cm-PAS*$_{S1}$) and right primary visual cortex (*cm-PAS*$_{V1}$).

- *Experiment 3* → depicted visual stimulus: touch stimulus (*cm-PAS*$_{touch}$) and no-touch stimulus (*cm-PAS*$_{no\text{-}touch}$):



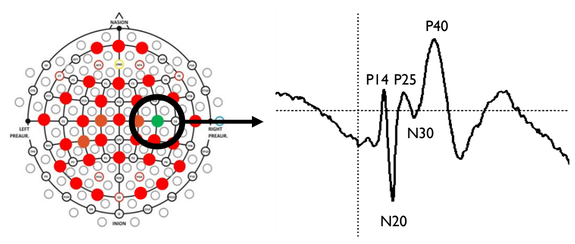
Timing and stimulation parameters unchanged

2-PDT *[all experiments]*

- *Body part tested:* thenar eminence of the left hand palm.
- *Dependent measures:* global performance and sensory threshold (d' prime).

SEPs RECORDING *[experiment 3]*

- *Activated nerve*: left-hand Median Nerve (MN)
- *Analysed EEG channel*: C4
- *Dependent measure:* peak amplitude



EXPERIMENTAL PROCEDURE

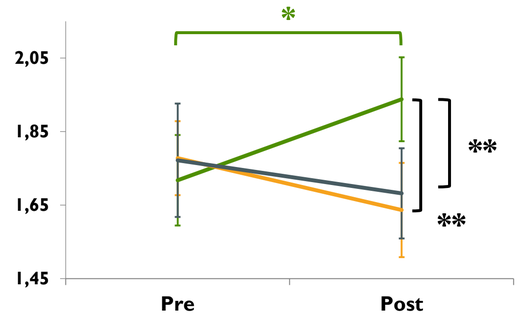
- *SEPs RECORDING* (pre) — t: 5' *[Only in Exp 3]*
- *2-PDT* (pre) — t: 15'
- ***cm-PAS*** — t: 25'
- *SEPs RECORDING* (post) — t: 5' *[Only in Exp 3]*
- *2-PDT* (post) — t: 15'

4 – RESULTS

* = p<0.05 ** = p<0.01 *** = p<0.001 *in all experiments post-hoc comparisons were corrected with Bonferroni*

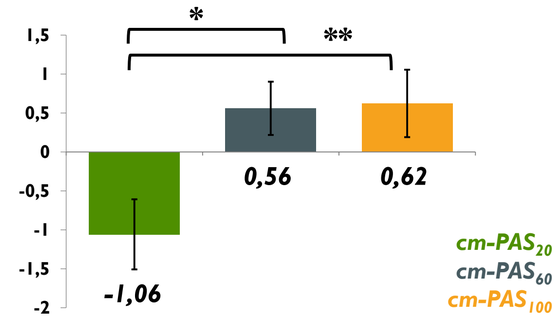
EXPERIMENT 1 → proving the **timing specificity** of the cm-PAS.

- *Design*: 3 counterbalanced sessions differing for the ISI used in cm-PAS between the paired stimulations.
- *Participants*: 16 subjects (9 F); age: 23.6 ± 3.1 years.
- *Results:* a) D-Prime (all distances collapsed)



Significant interaction 'ISI × Pre/Post' [$F_{(2, 30)}$= 8,38; p= 0.001]

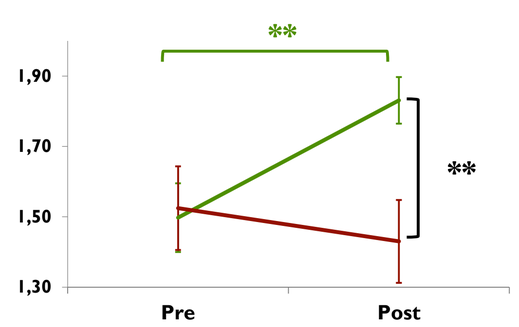
b) Sensory threshold changes (*mm*)



Main effect of ISI [$F_{(2, 30)}$= 6.55; p=0.004]

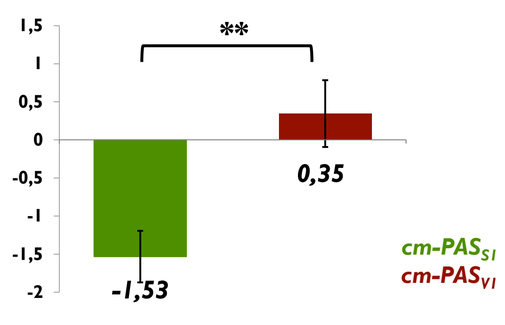
EXPERIMENT 2 → proving the **cortical specificity** of the cm-PAS.

- *Design*: 2 counterbalanced sessions differing for the cortical area stimulated during the PAS.
- *Participants*: 10 subjects (5 F); age: 23.7 ± 4.2 years.
- *Results:* a) D-Prime (all distances collapsed)



Significant interaction 'Area × Pre/Post' [$F_{(1, 9)}$= 10,976; p= 0.009]

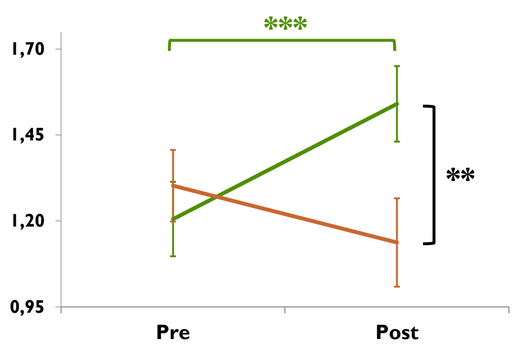
b) Sensory threshold changes (*mm*)



Significant paired samples t-test

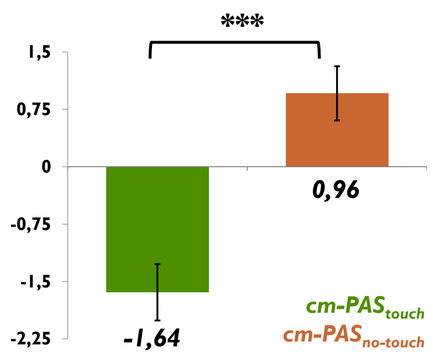
EXPERIMENT 3 → proving the **stimulus specificity** of the PAS and investigating **neurophysiological changing in S1** after its administration.

- *Design*: 2 counterbalanced sessions differing for the visual stimulus depicted in the PAS.
- *Participants*: 17 subjects (11 F); age: 23.6 ± 2.2 years.
- *Results:* a) D-Prime (all distances collapsed)



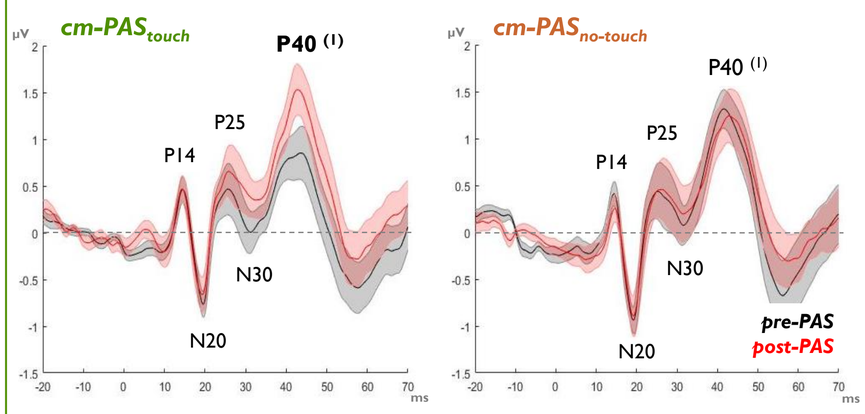
Significant interaction 'Condition × Pre/Post' [$F_{(1, 16)}$= 28.176; p<0.001]

b) Sensory threshold changes (*mm*)



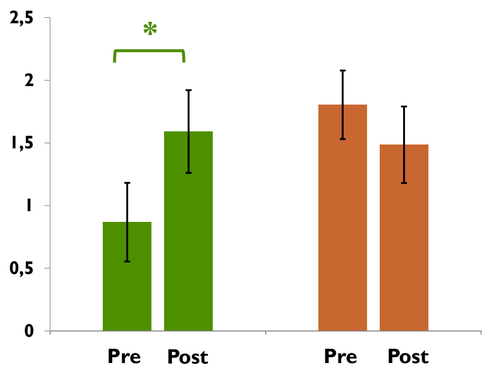
Significant paired samples t-test

c) Somatosensory Evoked Potentials (C4 electrode)



(1) P40 peak is the only SEPs component significantly modulated by cm-PAS

Significant interaction 'Condition × Pre/Post' [$F_{(1, 16)}$= 6,711; p= 0.02] for the **amplitude (µV) of SEPs' P40 peak**



5 – CONCLUSIONS

Experiment 1 and 2 show that cm-PAS successfully improved subjects' tactile acuity only when the ISI between the two paired stimulations is 20 ms and the TMS pulse is delivered over S1. *Experiment 3* enlightens both the selectivity of the visual responsiveness of S1 and that neurophysiological enhancements occur in later stages of S1 cortical elaboration.

Taken together, this evidence provides novel insight of the visual activity of S1, showing that our cm-PAS can induce plastic changes in somatosensory cortices, in line with an Hebbian associative learning rule. Furthermore, it also offers new insights on the neural substrates of the *Tactile Mirror System* and, in a broader perspective, of early visuo-tactile interactions in the primary (low-level) stages of sensory processing.

6 – REFERENCES

[1] Catmur, C., Press, C., & Heyes, C. (2016). Mirror Neurons from Associative Learning. In *The Wiley Handbook on the Cognitive Neuroscience of Learning* (pp. 1–45)
[2] Suppa, A., Quartarone, A., Siebner, H., Chen, R., Di Lazzaro, …, & Classen, J. (2017). The associative brain at work: Evidence from paired associative stimulation studies in humans. *Clinical Neurophysiology*, *128*(11), 2140–2164.
[3] Wolters, A., Schmidt, A., Schramm, A., Zeller, D., Naumann, M., …, & Classen, J. (2005). Timing-dependent plasticity in human primary somatosensory cortex. *The Journal of Physiology*, *565*(Pt 3), 1039–1052.

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