Research Project: **The influence of emotions on actions: Boosting brain network plasticity to ameliorate action control**

Theoretical background

Rapid interruption of ongoing actions is crucial to prevent the execution of undesired behavior. This is achieved via the integration of relevant signals into the neural processes to adjust or even stop it before its conclusion. Often mentioned examples include driving towards a crossroads, where the choice of executing or withholding an action (acceleration or braking) must be quick and should incorporate all information available. Importantly, in the heat of an emotional moment, affective states may profoundly affect cognitive functions, including action inhibition. Interestingly, both enhancement and impairment of action control by emotions have been observed in healthy participants (Battaglia et al., 2021). Therefore, a great deal of confusion characterizes our understanding of the influence of emotional stimuli on action control. As far as the potential neural responsible for the integration of action and emotion processing, one candidate is the action inhibition network, which guides the voluntary inhibitory process during action control (with neutral stimuli). Such a network is known to include the inferior frontal cortex (IFC) and the supplementary motor complex (SMA) and the subthalamic nucleus (SN) (Battaglia et al., 2021). Previous results suggest that the SMA-complex could be the cortical hub interfacing the limbic and the motor systems (Sagaspe et al., 2011). However, it is still a matter of debate whether and how these networks interface with the processing of emotional stimuli. Indeed, to test the hypothesis that the connectivity between the SMA and the primary motor cortex (M1) is crucial for action inhibition when emotional stimuli are presented, we will temporarily increase such connectivity to enhance the ability to suppress prepotent undesired actions facing emotional stimuli by means of corticocortical paired associative stimulation (ccPAS) protocol (Romei et al., 2016). This protocol represents an innovative Transcranial Magnetic Stimulation (TMS) paradigm able to induce spike-timing-dependent-plasticity when TMS paired pulses are repeatedly applied over interconnected cortical areas. Previous TMS studies have shown that similar synaptic strengthening (Hebbian plasticity) can be modeled in the human motor system over two interconnected motor areas (Romei et al., 2016). A recent study from our lab (Turrini et al., 2023) has demonstrated that ccPAS aimed at strengthening premotor-motor connectivity enhanced the human ability to perform a simple visuomotor behavioral task. However, previous TMS studies have limited their focus to simple motor tasks without testing the role of the premotor cortices in complex behavior, such as action inhibition facing complex behaviorally relevant stimuli (e.g., emotional expressions).

Aims and Hypotheses

The aim of the present project is to shed light on the way the human motor system makes humans able to inhibit prepotent responses in an emotional context. As the ultimate goal, by improving the functional connectivity of the action inhibition network, we aim at enhancing motor inhibitory abilities. We hypothesize that the functional connectivity between the supplementary motor cortex complex and the primary motor cortex might be the key component essential for the transformation of emotional experiences into motor inhibition.

Methods

Participants: sample size and justification of the sample size

A power analysis based on previously published studies (Romei et al., 2016) indicates that a sample size of 15 healthy participants is necessary to achieve a statistical power of > 95% (2-tailed = 0.05). Thus, 30 healthy volunteers will be tested in two experiments (see the Procedure section).

Tools

To measure action inhibition we will use a widely used paradigm called Stop Signal Task that we have widely employed in our previous works (Battaglia et al., 2022b, 2022a). In this task, participants are requested to respond to a go stimulus (i.e., discriminating an arrow orientation). However, sometimes, the go stimulus is followed by a stop signal (represented by either an emotional or a neutral stimulus) that requires participants to withhold the ongoing action. To measure the participant's performance, the stop-signal reaction time (SSRT), an index of reactive inhibition, will be computed. Estimated SSRT values will give the measure of the duration of the inhibitory process, with a lower value indicating a more efficient action control. To boost functional connectivity we will use an innovative TMS protocol called ccPAS, able to induce spike-timing-dependent-plasticity (Romei et al., 2016).

Procedure

Participants will be asked to perform the Stop Signal Task before and after the administration of the ccPAS protocol. In Experiment 1, the connectivity between the supplementary and the motor cortex (SMA-M1) will be boosted and this should induce higher action control facing emotional stimuli (experimental condition). In Experiment 2, we will boost the connectivity between the premotor and the motor cortex (IFC-M1). Since such connectivity is not supposed to be devoted to emotion perception, no changes in action control facing emotional stimuli are expected in this control experiment.

Statistical analyses

SSRT and reaction times (RTs) will be collected during the Stop Signal Task before and after the ccPAS administration. Analysis of variance (ANOVA) will be used to investigate differences within and between groups. Post-hoc analyses will be conducted with Newman-Keuls test, and the significance threshold will be set at $p < 0.05$.

Declaration of commitment to request ethical approval

All procedures have been already approved by the Bioethical Committee at UNIBO (2020), Prot. 126991 del 1/7/2020.

Expected results and Implications

If the functional connectivity between the SMA and M1 is critical for action inhibition when facing emotional stimuli, then strengthening their projections (Experiment 1) should increase performance in the emotional compared to neutral trials (i.e., lower SSRT after the SMA-M1 ccPAS), thus making participants more able to control their action inhibition in an emotional context. No changes in performance are expected after having increased the IFC-M1 connectivity (Experiment 2).
The key scientific highlight will be the discovery of the neural network subtending the interplay between actions and emotions. This knowledge will open the possibility to ameliorate our action control, even when usually emotional stimuli have a detrimental role on our cognition, by our innovative TMS protocol, which is able to boost the functioning of the action control network. Moreover, the lack of behavioral inhibition is a component of a variety of psychiatric conditions and the understanding of its neural dynamics could open the door to understanding how to modify these maladaptive mechanisms.

(6995 characters including spaces)

References

Battaglia, S., Cardellicchio, P., Di Fazio, C., Nazzi, C., Fracasso, A., & Borgomaneri, S. (2022a). Stopping in (e)motion: Reactive action inhibition when facing valence-independent emotional stimuli. *Frontiers in Behavioral Neuroscience*, *16*, 998714. https://doi.org/10.3389/fnbeh.2022.998714

Battaglia, S., Cardellicchio, P., Di Fazio, C., Nazzi, C., Fracasso, A., & Borgomaneri, S. (2022b). The influence of vicarious fear-learning in 'infecting' reactive action inhibition. *Frontiers in Behavioral Neuroscience*, *16*, 946263. https://doi.org/10.3389/fnbeh.2022.946263.

Battaglia, S., Serio, G., Scarpazza, C., D'Ausilio, A., & Borgomaneri, S. (2021). Frozen in (e)motion: How reactive motor inhibition is influenced by the emotional content of stimuli in healthy and psychiatric populations. *Behaviour Research and Therapy*, *146*, 103963. https://doi.org/10.1016/j.brat.2021.103963

Romei, V., Chiappini, E., Hibbard, P. B., & Avenanti, A. (2016). Empowering reentrant projections from V5 to V1 boosts sensitivity to motion. *Current Biology*, *26*(16), 2155–2160. https://doi.org/10.1016/j.cub.2016.06.009

Sagaspe, P., Schwartz, S., & Vuilleumier, P. (2011). Fear and stop: A role for the amygdala in motor inhibition by emotional signals. *NeuroImage*, *55*(4), 1825–1835. https://doi.org/10.1016/j.neuroimage.2011.01.027

Turrini, S., Bevacqua, N., Cataneo, A., Chiappini, E., Fiori, F., Candidi, M., & Avenanti, A. (2023). Transcranial cortico-cortical paired associative stimulation (ccPAS) over ventral premotor-motor pathways enhances action performance and corticomotor excitability in young adults more than in elderly adults. *Frontiers in Aging Neuroscience*, *15*, 1119508. https://doi.org/10.3389/fnagi.2023.1119508

Plan of activities

Research environment: the proposed project will be carried out at the Center for studies and research in Cognitive Neuroscience in Cesena.

Project activities: literature review to acquire relevant theoretical knowledge and to define stimulation parameters and behavioral procedures, recruitment of participants, execution of a pilot study to assess experimental duration and participant's compliance, data collection and analysis, writing of a draft of the main findings to be submitted to a scientific journal and research dissemination at national/international congresses.

Training activities: readings, discussions with the supervisor, direct involvement in lab meetings, attendance of lectures and workshops, revision of manuscripts; activities aimed at acquiring: 1) theoretical knowledge about key models and thematic areas related to cognitive neuroscience of action control; 2) skill for designing and conducting scientific research projects, data analysis and use of non-invasive brain stimulation procedures; 3) writing and oral communication skills for scientific dissemination.

Timing of activities: literature search designing and piloting (Oct 2023 – Dec 2023); Data collection and analysis (Jan 2024 – July 2024); Dissemination (June 2024 – Oct 2024).

Feasibility of the project: the project is highly feasible and involves low risks. The supervisor have acquired extensive expertise on the methods and have already conducted several studies using TMS. Procedures have been already approved by the ethical committee at UNIBO. All the tools and research

materials have been already acquired. Based on previous studies we predict mid/large effect sizes; therefore, an adequate sample can be acquired in less than 7 months.

(3468 characters including spaces)