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Motor overload: GABAergic index of parallel buffer costs

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Everyday life actions are continuously adjusted to the context and halted promptly when the environment requires to switch from the current action to a different one. Action changing/adaptation is a multicomponent process that effectively optimizes the chaining of different sub-actions. This process is based on different control strategies that operate on a continuum, adopting either serial (i.e., a task goal is activated after the previous one has been carried out) to parallel (i.e., multiple goals active at the same time or overlay mode) strategies [1]. In the parallel strategy, the different task sub-goals share the same limited processing capacity, ultimately hampering response speed. Otherwise, the serial strategy produces no interference between sub-goals. One early component of the action changing process is the preliminary stop of the ongoing action. This stopping has been related to the activity of inhibitory GABAergic circuits in the motor system, that may account for individual differences in action stopping performance [2,3]. However, to date, it is unclear if and how GABAergic neurotransmission relates to individual strategies adopted in action changing.

Here we asked participants to perform a standard action changing task [1] while, in a separate session, we measured GABAergic-related indices by means of TMS. Specifically, we used paired-pulse TMS protocols to measure short-interval and long-interval intracortical inhibition (SICI/LICI). While SICI is mediated by post-synaptic potentials via fast ionotropic GABAa receptors, LICI seems to reflect inhibitory post-synaptic potentials produced via slower metabotropic GABAb receptors [4,5]. We also measured cortical silent periods (cSP) which has been associated to GABAb-based neuromodulation and corticospinal excitability (glutamatergic), both measured via single pulse TMS during active muscle contraction or at rest respectively [4,5]. In general, GABAergic indices are modulated prior and during volitional action and have been shown to be differentially modulated by specific motor tasks [4,5].

The behavioral task adopted here is the well-established stop-change paradigm (Fig. 1) [1,6,7]. We tested 27 right-handed participants (12 males; mean age: 25.34, SD: ±3.8). Participants are required to stop an ongoing response to a GO stimulus whenever an occasional STOP (~33%) signal is presented. The STOP signal is then followed by a CHANGE stimulus, signaling participants to change to an alternative response. Crucially, the interval between the STOP and the CHANGE stimulus (stop-change delay; SCD) is manipulated in such a way that the two stimuli occur either simultaneously (0 ms: SCD0) or with a short delay (300 ms: SCD300). For SCD0, subjects can process the actions either serially or in parallel; at SCD300, the actions are necessarily processed in a serial manner. Reaction times (RTs) to the GO stimuli reflect response execution efficiency. The difference between RTs and the STOP Signal Delay (SSD), reflect the stop-signal reaction time (SSRT) performance. Combining data from the stop-change trials we can extract another parameter, the s-Slope, which allows quantifying along a continuum the underlying strategy used to process more actions [1,6,7].

In a separate experimental session, performed within two days from the behavioural task, we measured the individual responses to the different TMS paired pulse protocols in order to investigate possible correlations among behavioral and neurophysiological responses.

EMG responses were measured from the right first dorsal interosseous muscle (FDI) and TMS delivered over the left M1 using a monophasic pulse-shape with a posterior-anterior current direction. Different protocols (i.e., SICI, LICI, cSP) were recorded in separate randomized blocks.

For SICI, two different ISIs have been employed: 1 and 3 ms ($SICI_{1ms}$, $SICI_{3ms}$). These two ISIs are believed to reflect different inhibitory circuits [8]. While $SICI_{1ms}$ is thought to represent a mechanism of synaptic inhibition that may involve refractoriness of neural membranes, $SICI_{3ms}$ instead is considered the expression of synaptic inhibition mediated by the GABAa receptor.

SICI and LICI were calculated as a ratio of the mean Motor Evoked Potentials obtained by a single pulse. Corticospinal excitability was measured with a single pulse set at 120% of the rMT. The cSP was measured with pulses delivered at 120% of the active Motor Threshold (rMT). Trials were separated by a random 5–6 s interval.

All correlations, tested using Pearson's correlation coefficient, are reported in Supplementary Table1. We found that SICI strongly correlated with individual performances in the stop-change task. Specifically, we found that SSRT was correlated with $SICI_{1ms}$ ($r = 0.537$, $p = .004$) and with $SICI_{3ms}$ ($r = 0.464$, $p = .015$). Meanwhile, only $SICI_{1ms}$ correlated with the strategy adopted by participants (s-Slope; $r = 0.448$, $p = .019$). No other correlations were found to be significant for LICI and cSP protocols (Fig. 1). Results

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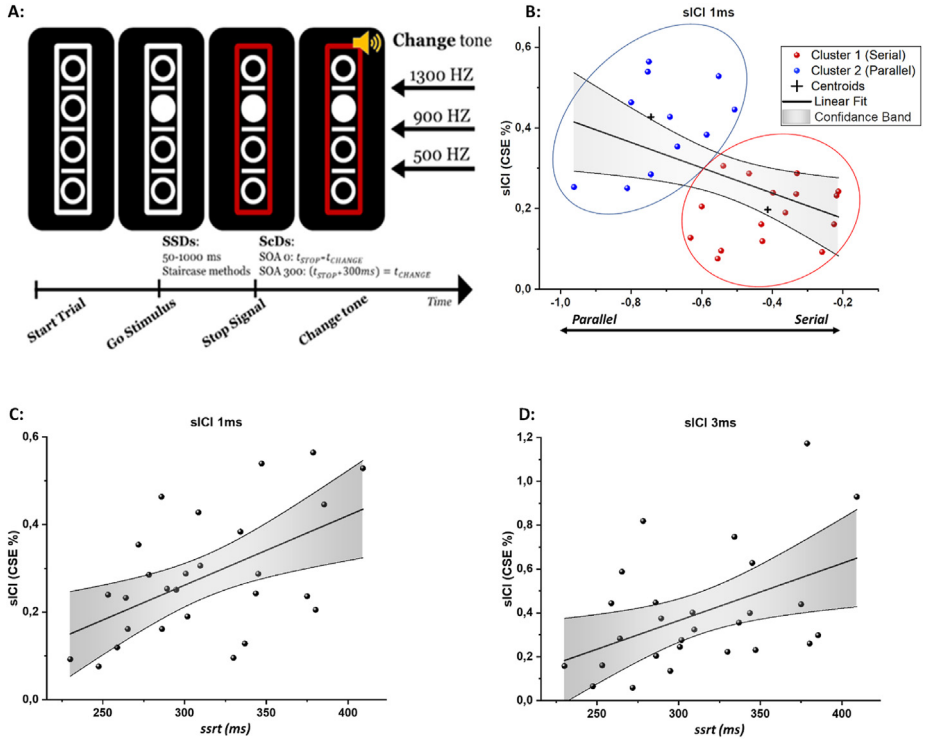

Fig. 1. Panel A: Schematic illustration of the stop–change task. GO trials end after the first response to the GO stimulus. SC trials end after the first response to the CHANGE signal. The stop-signal delay (SSD) between the onset of the GO stimulus and the STOP signal was adjusted using a staircase procedure. The CHANGE signal was presented after a stop-change delay (SCD) of either 0 ms or 300 ms. CHANGE stimuli were associated with one of the three reference lines (white horizontal lines in the rectangle containing the dots). Panel B: Cluster plot and regression line (in black) between short intracortical inhibition (sICI) at 1 ms and s-Slope. Panel C: Scatter plot, regression line, and 95% confidence band of sICI at 1 ms by stop-signal reaction time (ssrt). Panel D: Scatter plot, regression line, and 95% confidence band between sICI at 3 ms and ssrt.

were confirmed by a cluster analysis to split participants in the two strategies to compare their GABAergic modulations (Further details are available in the Supplementary Materials).

Our results replicate previous data suggesting a relationship between SICI and stopping performance [2,3]. Furthermore, we provide novel evidence supporting the idea that SICI at different ISIs at 1 and 3 ms holds information related to the activity of two GABAa-mediated inhibitory sub-process. Indeed, previous studies suggest that SICI may consist of two phases of inhibition that can be contaminated by superimposed periods of facilitation (I-wave facilitation) [8–10]. Despite further studies are still required to identify the exact mechanisms underlying ISIs differences in SICI, we found a specific relationship between the GABAergic activity mediated by $SICI_{1ms}$ and the participant strategy adopted. This result indicates how the motor plan adopted by participants was more prone to follow a serial or a parallel strategy. Indeed, our data revealed the existence of a specific association among resting-state SICI at 1 ms and the tendency to adopt a parallel strategy.

These findings suggest an association between the recruitment of specific inhibitory neuronal circuitry in the motor system and the costs associated to parallelizing multiple goals at the same time. GABAergic neurotransmission may however be one aspect of the different neurobiological factors modulating the balance between alternative processing modes [6]. Specifically, GABAergic neurotransmission may act in synergy with other neuromodulating factors exerting global activating effect on cognitive functioning (i.e., vigilance, arousal, attention, motivation, etc.) such as norepinephrine, that has similarly been observed to contribute to actions cascading strategies [7].

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Declaration of competing interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.07.061.

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Pasquale Cardellicchio*
IIT@UniFe Center for Translational Neurophysiology, Istituto Italiano di Tecnologia, Via Fossato di Mortara, 17-19, 44121, Ferrara, Italy

Giacomo Koch
Department of Neuroscience and Rehabilitation, Section of Physiology, Università di Ferrara, Via Fossato di Mortara, 17-19, 44121, Ferrara, Italy

Experimental Neuropsychophysiology Lab, Fondazione Santa Lucia IRCCS, Via Ardeatina 306, 00179, Rome, Italy

Luciano Fadiga[1], Alessandro D'Ausilio[1]
IIT@UniFe Center for Translational Neurophysiology, Istituto Italiano di Tecnologia, Via Fossato di Mortara, 17-19, 44121, Ferrara, Italy

Department of Neuroscience and Rehabilitation, Section of Physiology, Università di Ferrara, Via Fossato di Mortara, 17-19, 44121, Ferrara, Italy

* Corresponding author.
E-mail address: pasquale.cardellicchio@iit.it (P. Cardellicchio).

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[1] These authors contributed equally to the manuscript.