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Replicable effect of cortical-paired associative stimulation on response inhibition as a function of age

Dear Editor

How quickly we stop at a traffic light determines our survival. Similarly, how efficiently one can dodge a craving thought for a pint of beer could define one's relapse probability. Response inhibition, a form of impulsivity, measures one's ability to interrupt an ongoing action, and is central to neuropsychiatric disorders [1,2]. Using cortico-cortical paired associative stimulation (cc-PAS) with transcranial magnetic (TMS) pulses, we targeted the right pre-supplementary motor area (preSMA) and right-inferior frontal cortex (rIFC). We previously showed an improvement in response inhibition as a function of age [3] using the stop-signal task [1]. Repeated pairs of pulses over two cortical regions induce changes in excitability and functional interaction due to spike time-dependent plasticity mechanisms [4]. Specifically, response inhibition improved in older individuals when the rIFC pulse preceded the preSMA pulse by 4milliseconds [3]. Here, we address the problem of reproducibility, a significant issue in TMS studies, by assessing the 4 ms cc-PAS protocol in a different, larger group of healthy volunteers with a broader age range.

We recruited 40 healthy volunteers (aged 22–59) through posters and emails to a healthy volunteer database, out of which 3 participants were excluded (software malfunction, early study termination). Exclusion criteria included TMS contra-indications, serious neurological disorders, or hearing impairments. The Cambridge South Research Ethics Committee approved the study, and informed written consent was obtained. The study consisted of a single stimulation session of cc-PAS over the rIFC and preSMA, with pulses paired 4 ms apart, delivered using two Magstim-200^2 machines and two figure-of-eight 70mm coils (The Magstim Company Ltd.,Spring Gardens,Whitland,UK). The same targets [3] were used based on a meta-analysis on response inhibition [5]: r-IFC: x,y,z (48,16,16); preSMA: (10,10,60) (Montreal Neurological Institute coordinates in mm). The right IFC coil was 20° angle to the coronal plane (Fig. 1B) with the handle pointing anteriorly and the right preSMA perpendicular to the midline (Fig. 1B).

Stimulation accuracy was monitored with neuro-navigation (Brainsight; Rogue Research Inc., Montreal,Quebec,Canada). Resting motor threshold (RMT) was identified with a single TMS pulse to the contralateral motor hotspot, corresponding to the non-dominant hand's first dorsal interosseous muscle. RMT was defined as the lowest intensity stimulation eliciting 5/10 motor-evoked potentials with amplitude >50$\mu V_{peak\text{-}peak}$. A total of 100 pulse pairs at 0.2 Hz (8.3-min duration) were delivered with an intensity of 120% RMT.

We assessed response inhibition using the stop-signal task(-Cambridge Cognition, Cambridge, UK) at baseline and immediately after cc-PAS, well within the 30-min active window for cc-PAS [4]. Participants saw a go-signal (left or right-pointing arrow) and pressed one of two buttons with their right or left index finger (Fig. 1C) and withheld responding to stop-signal(audio tone). A lower stop-signal reaction time (SSRT = median go reaction time − stop-signal delay) indicates an efficient inhibitory cancellation of the ongoing motor response. We conducted a non-parametric independent samples *t*-test for non-normally distributed data (Kolmogorov-Smirnov test) in SPSSv27.

In line with our previous analysis [3], we categorised the participants into either older (n = 17, age in mean and SD: 44.5 ± 9.2) or younger (n = 20, age: 25.3 ± 2.9) group based on the median age of 30 years. The difference between the SSRT (in milliseconds) at baseline ($SSRT_{baseline}$: young = 153.33 ± 36.43, old = 179.15 ± 58.13) and after stimulation ($SSRT_{ccPAS}$: young = 157.33 ± 49.58, old = 152.65 ± 43.55) was calculated ($SSRT_{ccPAS\text{-}baseline}$: young = 3.99 ± 41.88, old = −26.5 ± 28.11). A Mann-Whitney *t*-test showed a significant (U = 102, p = 0.03) improvement in stopping in older adults post-stimulation compared to baseline.

We successfully replicate our earlier findings in which cortico-cortical stimulation of rIFC 4 ms before preSMA improved response inhibition in older individuals. Our 'older' group is relatively young and may limit generalisability. Cortical excitability measures [6], and plasticity changes induced by PAS decline with age, particularly above 60 [7]. Age-related anatomical differences in brain volume may further influence the measures, efficacy, and diffusion of the TMS pulse delivered at the scalp, an effect more prominent in older age. However, our findings demonstrate the opposite effect– an increase in cortical excitability using this ccPAS protocol in an older population. Our ccPAS protocol is hypothesized to increase the connectivity strength of the preSMA-STN pathway, thus improving performance. This preSMA-STN tract predicts SSRT, particularly in older individuals [8]. Furthermore, the ccPAS protocol might further improve dynamic modulation and efficiency within the frontoparietal network [9], decreasing with age.

These results strengthen our cc-PAS protocol's validity in modulating cortico-cortical and cortico-subcortical networks as a function of age. These findings have implications for obsessive-compulsive disorder and addiction disorders, commonly characterized by impairments in response inhibition. In future, we plan to combine this cc-PAS protocol with task-based imaging to investigate and quantify the connectivity changes between STN-preSMA and STN-rIFC, respectively, in young and over the age of 60.

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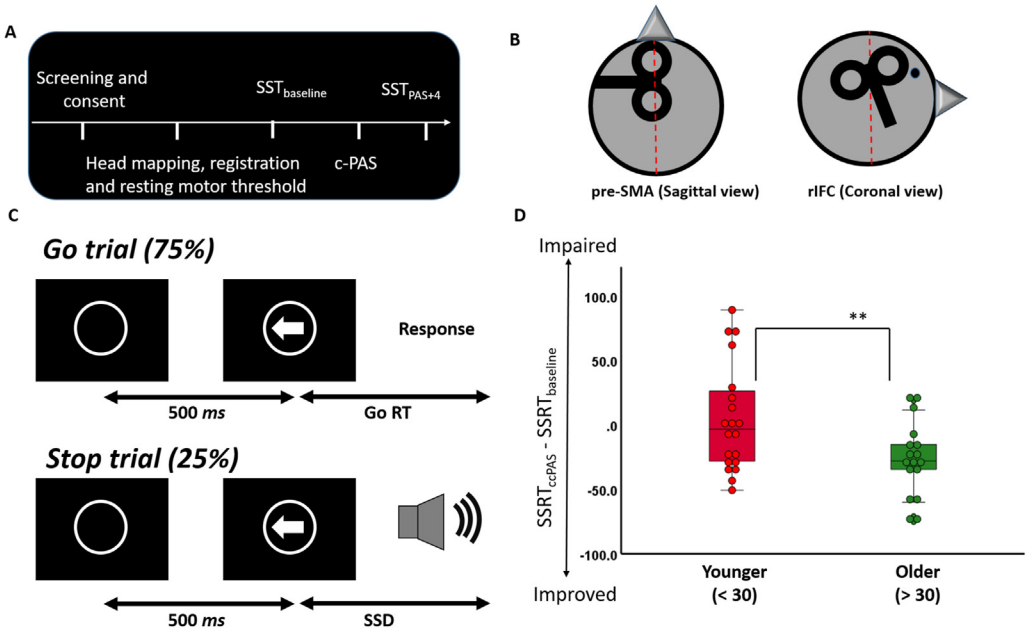

Fig. 1. Shows the experimental design and results of the stop-signal task (SST) from cortico-cortical paired associative stimulation (ccPAS) protocol: (A) the timeline of the study, (B) the coil positions for the pre-supplementary motor area (pre-SMA) and right Inferior frontal cortex (rIFC) in sagittal and coronal view respectively, (C) the schematic representation of the SST, and (D) box plot representing the mean difference (with standard error) of the reaction time during the task at baseline ($SSRT_{baseline}$) and ccPAS stimulation ($SSRT_{ccPAS}$) condition. $^{**}p < 0.05$.

Authorship contribution statement

AM: Experiment design, recruitment and testing, data analysis, and manuscript preparation.

KT: Experiment design, recruitment and testing, and manuscript preparation.

TP: Experiment design, manuscript preparation.

VV: Experiment design, recruitment, data analysis, and manuscript preparation.

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Declaration of competing interest

All authors declare no potential conflict of interest.

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