The Supplementary Motor Area and Automatic Cognitive Control: Lack of Evidence from Two Neuromodulation Techniques

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Abstract

■ The SMA is fundamental in planning voluntary movements and execution of some cognitive control operations. Specifically, the SMA has been known to play a dominant role in controlling goal-directed actions as well as those that are highly predicted (i.e., automatic). Yet, the essential contribution of SMA in goal-directed or automatic control of behavior is scarce. Our objective was to test the possible direct role of SMA in automatic and voluntary response inhibition. We separately applied two noninvasive brain stimulation (NIBS) inhibitory techniques over SMA: either continuous theta-burst stimulation using repetitive transcranial magnetic stimulation or transcranial static magnetic field stimulation. Each NIBS technique was performed in a randomized, crossover, sham-controlled design. Before applying NIBS, participants practiced a go/no-go learning task where associations between stimulus and stopping behaviors were created (initiation and inhibition). After applying each NIBS, participants performed a go/no-go task with reversed associations (automatic control) and the stop signal task (voluntary control). Learning associations between stimuli and response initiation/inhibition was achieved by participants and therefore automatized during training. However, no significant differences between real and sham NIBS were found in either automatic (go/no-go learning task) or voluntary inhibition (stop signal task), with Bayesian statistics providing moderate evidence of absence. In conclusion, our results are compatible with a nondirect involvement of SMA in automatic control of behavior. Further studies are needed to prove a noncausal link between prior neuroimaging findings relative to SMA controlling functions and the observed behavior. ■

INTRODUCTION

Cognitive control involves a reciprocal balance between initiation and inhibition of actions to flexibly adapt behavior. Uncertainty and learning may adjust performance using top–down goal-directed, intentional, and flexible operations over ongoing behavior (Logan & Gordon, 2001; Miller & Cohen, 2001). However, with repetition and practice, cognitive control can be easily executed in a bottom–up, fast, and cost-free efficient manner (Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Verbruggen & Logan, 2008) to be used in reducing approach to reward (Weinbach, Keha, Leib, & Kalanthroff, 2020; Adams, Lawrence, Verbruggen, & Chambers, 2017) or risk-taking (Xu, Wu, Chen, Wang, & Xiao, 2020). Given the large benefits of automatic performance, human behavior tends to be organized as much as possible into automatic routines even for cognitive control. Response inhibition, conflict detection, or action selection between competing options can be utilized in a well-organized manner and learned to become part of an automatic "learned" system (Verbruggen, Best, Bowditch, Stevens, & McLaren, 2014; Verbruggen & Logan, 2008). Yet, goal-directed and automatic processes are not mutually exclusive (Linnebank, Kindt, & De Wit, 2018; Eryilmaz et al., 2017; Morris et al., 2016; Jasinska, 2013) and probably interact to support controlling systems in changing external or internal variables (Verbruggen et al., 2014). Importantly, automatic control processes may rely on both (i) voluntary processes to execute inhibition that via repetition and trial-and-error (mediated with reward/punishment feedback) can be associated with a particular response, and (ii) with automatic control operations activated involuntarily, such as sudden unexpected events (less dependent on associative learning; Diesburg & Wessel, 2021). Hence, cognitive control may be initially triggered in a deliberate and goal-directed manner modulated by associative learning (top–down) shifting into automatic, stimulus-driven fashion (bottom–up) after considerable practice.

Functional neuroimaging studies report a large distributed network of cortical and subcortical regions active during response initiation and inhibition (Isherwood, Keuken, Bazin, & Forstmann, 2021; Swick, Ashley, & Turken, 2011). Initiation of actions activates a premotor–

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striato–pallidal–motor cortical circuit (Aron & Poldrack, 2006), whereas stopping includes ACC, SMA and pre-SMA, inferior frontal gyrus (IFG), subthalamic nucleus, or striatum (Maizey et al., 2020; Suda et al., 2020; Rae, Hughes, Anderson, & Rowe, 2015; Watanabe et al., 2015; Yu, Tseng, Hung, Wu, & Juan, 2015; Albares et al., 2014; Obeso et al., 2013; Smittenaar, Guitart-Masip, Lutti, & Dolan, 2013; Jahfari et al., 2012; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Aron, Behrens, Smith, Frank, & Poldrack, 2007), typically explored using stop signal or go/no-go tasks. Among these circuitries, the above regions participate in parallel exerting controlling functions to adjust behavior accordingly, by initiation or inhibition of responses in a goal-directed manner. The transition from goal-directed to automatic control of behavior has received less attention in the field. Some neuroimaging (fMRI and EEG) accounts link cortical regions such as the SMA or IFG in processing automated control and response selection (Albares et al., 2014; Smittenaar et al., 2013; Lenartowicz, Verbruggen, Logan, & Poldrack, 2011). Results are interpreted as a SMA-dominant role in creating task-sets and rule programming (Forstmann et al., 2008, 2010; Vallesi, McIntosh, Alexander, & Stuss, 2009; Nachev, Kennard, & Husain, 2008; Rushworth, Walton, Kennerley, & Bannerman, 2004) and modulating behavior toward contextual changes, motor planning, or stimulus-triggered responses (Albares et al., 2014; Obeso et al., 2013; Smittenaar et al., 2013; Nachev et al., 2008). Although these functions are all essential to successfully adapt in predicted contexts (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Shiffrin & Schneider, 1984), the essential role of each brain region in automatic control is uncertain.

Noninvasive brain stimulation (NIBS) is arguably one of the most direct ways to test brain–behavior relationships. Previous accounts using brain stimulation have proven useful to determine the essential contribution of SMA in organized behavior during execution of learned motor sequences (Wymbs & Grafton, 2013; Gerloff, Corwell, Chen, Hallett, & Cohen, 1997), motor planning (Pineda-Pardo et al., 2019), or implicit motor learning (Shimizu et al., 2020; Wymbs & Grafton, 2013). Hence, combined use of NIBS and behavioral paradigms can help elucidate what precise contribution SMA may play in automated cognitive control.

In the present study, we examined the effect of SMA modulation in bottom–up automatic control of response initiation and inhibition. Our objective was to investigate the role of the SMA in cognitive control by dissociating its function in learned automatic inhibition and nonlearned, goal-directed inhibition. To this end, we designed a go/no-go learning task that captures initial acquisition of stimulus–response associations (initiation and inhibition) through a practice period and later reversed to test the level of automaticity (mixed with new response learning). Meanwhile, to obtain nonlearned, goal-directed measures of cognitive control, we used a classic stop signal task (SST). Two inhibitory NIBS were selected to target SMA: We first applied a continuous theta-burst stimulation protocol of repetitive transcranial magnetic stimulation (rTMS) in a first experiment, followed by transcranial static magnetic field stimulation (tSMS) in a second experiment. We hypothesized that both rTMS and tSMS of SMA would specifically deteriorate automatic control response, while sparing learning and goal-directed inhibition.

METHODS

Experiment 1

Participants

Seventeen healthy, right-handed volunteers (6 men, 11 women), aged 22–36 years (27.5 ± 4.6 years) participated in the study, all of whom met the TMS safety criteria (Rossi et al., 2009). Sample size was determined based on similar studies using neuromodulation techniques to measure within-subject behavioral changes with rTMS (Emanuel, Herszage, Sharon, Liberman, & Censor, 2021; Zack et al., 2016). Based on related studies, we included similar sample sizes including 17 participants.

Design

We used a randomized, crossover, sham-controlled design. Participants received both real and sham rTMS over SMA (sham stimulation with coil tilted 90°). Sessions were separated at least 1 week apart using counterbalanced order and random assignment. Participants were told that they would receive both real and sham stimulation in two different sessions, but they were blinded to the condition to which they were assigned in each session. We tried to minimize the placebo confound by selecting participants naive to the rTMS technique.

Experimental steps were conducted as follows: target localization using infrared neuronavigation system; training phase of behavioral tasks; NIBS application: rTMS (real or sham); and test phase of go/no-go task and the SST. Participants were individually tested in a quiet room and sat at a comfortable distance from the screen (60 cm). Task duration was about 10 min per task for 20 min. It is known that the effect of stimulation is active at least for 30 min (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Therefore, we are confident that both tasks were performed under the effects of NIBS.

Experiment 2

Participants

Sample size was based on a similar tSMS experiment (Pineda-Pardo et al., 2019), including 28 participants (14 men), aged 21–33 years (24 ± 3.2 years), in the tSMS experiment.

Design

Participants received real tSMS and sham over SMA. A protocol identical to the one of Experiment 1 was used in the tSMS experiment. In contrast, in the tSMS procedure, guessing the stimulation session is a difficult task given the procedure was identical between real and sham sessions.

The study (including both experiments) was approved by the local ethics committee (Comité Ético de Investigación de HM Hospitales). Before study commencement, informed consent was obtained from all participants.

Behavioral Paradigms

Behavioral paradigms were identical for both experiments. A go/no-go learning task was designed based on a previous study (Verbruggen & Logan, 2009) to create stimulus–response associations of initiation and inhibition of responses (Figure 1A). In contrast to their previous design (Verbruggen & Logan, 2009), we opted to select images rather than words to avoid potential semantic processing and set the focus in action selection mechanisms. The task included a training phase and a test condition. In the training phase, participants were presented with a series of neutral stimuli (objects and animals; obtained from Foroni, Pergola, Argiris, & Rumiati, 2013). Instructions asked participants to respond as quickly as possible (pressing the space bar) to a given category (e.g., animal images, 50%) and to withhold their response to the other category (e.g., object images, 50%). The equal distribution of conditions in the go/no-go task is not the standard approach when exploring prepotent and inhibitory

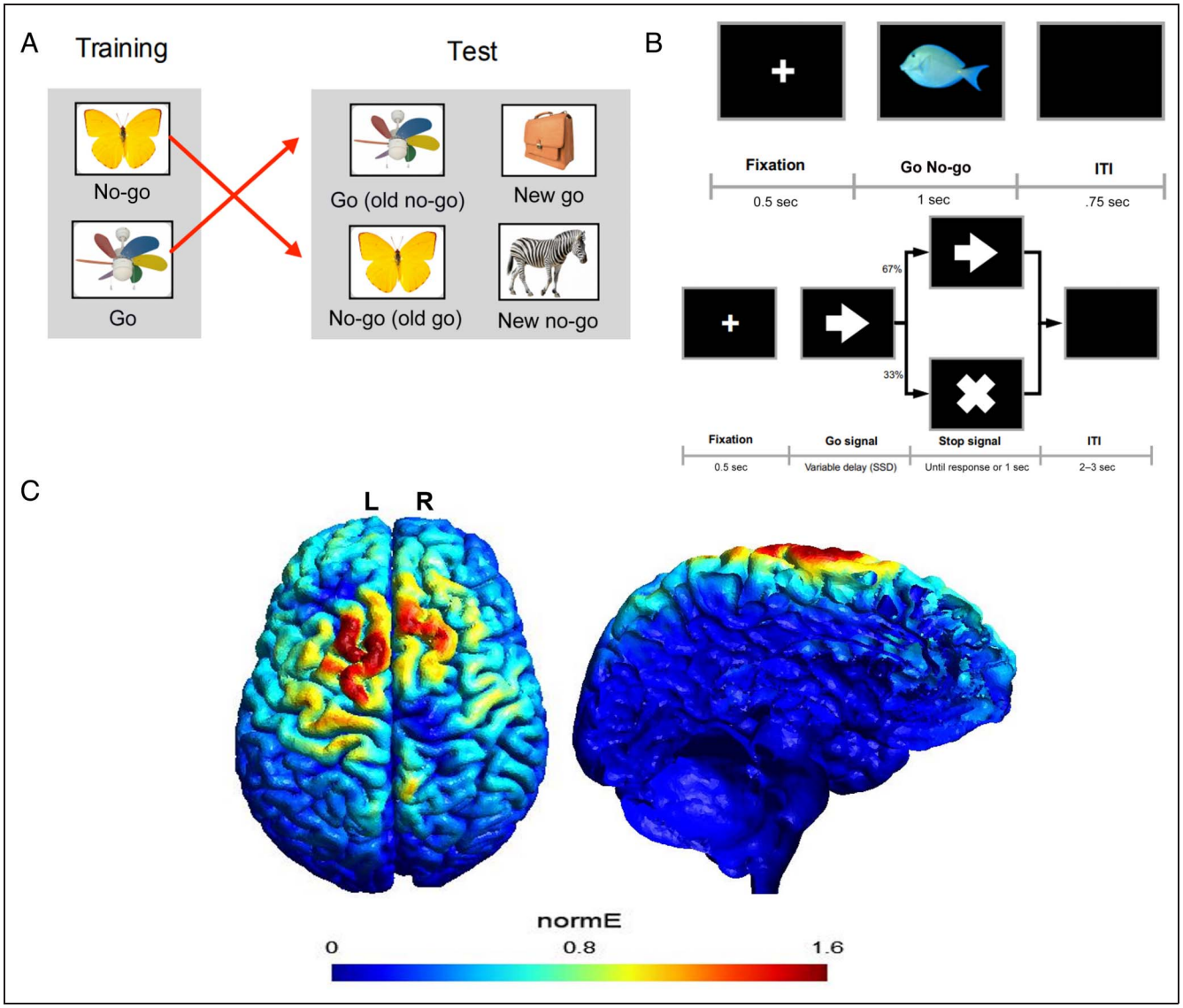

Figure 1. Go/no-go learning and stop signal task design and SimNIBS simulation. (A) Go/no-go task conditions. (B) Single trial examples on the go/no-go learning (top) and SSTs (bottom). (C) Results of SimNIBS simulation of the TMS over the SMA in a representative participant. Axial (left) and sagittal (right) views of the electric field. NormE = norm electric field.

behaviors (Wessel, 2018), but our motivation for such a choice was to have equal learning trials per condition. Feedback was displayed if an error was made. The training phase consisted of six blocks of 64 trials each (512 trials in total).

In the test phase, participants were explicitly instructed to reverse the learned associations between go and no-go responses. If animal images corresponded to go trials, in the test phase, they would require a no-go response (and vice versa for object images; Figure 1A). To compare the effects of previously learned associations with new items and possible neuromodulation disruptive effects on learning, a new set of stimuli were added in each stimuli type. We termed "old stimuli" those previously associated to no-go trials that turned into go trials during the test phase. In addition, "new stimuli" were the new images added to compare against old stimuli. The test phase included three blocks of 64 trials each (half go and half no-go trials with 50% new stimuli).

All trials initiated with a fixation cross in the center of the screen (500 msec) followed by the stimulus (go or no-go; maximum limited-hold of 1000 msec; Figure 1B). Between each block, speed and accuracy feedback was displayed to favor task engagement and self-monitoring of learning performance. During training, we focused on go reaction time (GoRT) and probability of responding in no-go trials (p(respond|no-go)). In the test phase, we considered GoRTs for old (previously no-go stimuli) and for new stimuli.

The SST was used to account for goal-directed inhibition of behavior (Logan, Cowan, & Davis, 1984). The task consisted in a combination of go and stop trials. Following a fixation cross (500 msec), a go signal (left or right pointing white arrow) was presented on a computer screen and participants had to respond as accurately as possible to the direction of the arrow (go stimulus); a "left arrow" required an index finger response; and a "right arrow," a middle finger response. On stop trials, the go stimulus was followed by a stop signal (cross) and participants were instructed to withhold their response (Figure 1B). Presentation of stop signals varied in time using a staircase procedure with variable stop signal delays (SSDs; 50–200 msec) and changed based on the participant's response: If a successful inhibition was produced, subsequent SSD increased by 50 msec; if failed, however, the subsequent SSD decreased by 50 msec. Three blocks were performed with 16 stop and 48 go trials per block (total 192 trials). We computed the average SSD obtained for each participant at the point of 50% P(inhibit). The stop signal reaction time (SSRT) was obtained using the integration method to avoid overestimation of SSRT and replacing go omission trials (Verbruggen et al., 2019). We also collected data about GoRTs and StopRespond RTs (stop trials on which participants failed to inhibit and responded). Data from five participants were not collected because of computer hardware failure. Tasks were designed and performed using E-Prime 2.0 (Psychology Software Tools).

NIBS Techniques

Experiment 1

The rTMS protocol was applied using a Magstim Rapid^2 Plus^1 stimulator (Magstim). To obtain stimulation thresholds for the SMA, we registered motor evoked potentials from the left first dorsal interosseous to localize the right hand motor area, using a figure-of-eight coil with the handle pointing 45° backward. The starting point was at 2 cm anterior and 4 cm lateral to Cz. The stimulation coil was then moved in steps of 0.5 cm to find the "hot spot." We used a stimulation output intensity of 80% of each individual's active motor threshold (AMT) from the right motor cortex. The AMT was defined as the minimal stimulus intensity required to produce motor evoked potentials of around 200-μV amplitude in at least 5 of 10 consecutive pulses while the muscle was active. Continuous theta-burst stimulation (TBS) was applied with a 40-sec train of uninterrupted TBS (600 pulses) known to reduce cortical excitability for a period of 30 min (Huang et al., 2005). Every TBS was repeated at a 5-Hz rate resulting in 200 bursts with 600 pulses at 80% of the AMT of each participant, following safety guidelines (Wassermann et al., 1996). Stimulation intensity across participants was 34.6 ± 6.4% (range 44–26%). For SMA stimulation, the coil was placed tangentially to the selected spot. For sham stimulation, the coil was tilted vertically over SMA with a 90° inclination ensuring the magnetic field was not pointed toward the participant's scalp. We simulated the magnetic TMS field using "Simulation of Non-Invasive Brain Stimulation" (SimNIBS; Thielscher, Antunes, & Saturnino, 2015) to cross validate our target and magnetic field during our SMA stimulation protocol (see Figure 1C). According to the simulation, the selected setup elicited a strong electric field within the posterior part of the superior frontal gyrus, representing the SMA. Moreover, we notice the extension of the field also involved more anterior region corresponding to pre-SMA and a part of the contralateral SMA, even if with less intensity (Figure 1C).

Experiment 2

For the tSMS protocol, we used a cylindrical nickel-plated (Ni-Cu-Ni) NdFeB magnet of 45-mm diameter, 30 mm of thickness, and 360 g (MAG45r, Neurek SL) with south magnetic field polarity. Sham stimulation was performed with a nonmagnetic stainless steel cylinder that was identical in appearance to the real magnet. The cylindrical magnet or sham device were placed over the participant's scalp and centered on the SMA target. Participants were seated comfortably in a semidarkened room and were instructed to refrain from speaking and to remain awake while in a calm state. The duration of the tSMS application was chosen based on our recent findings showing that a 30-min tSMS over the motor cortex reduces corticospinal excitability for at least 30 min after the end of the application and modulates behavior (Pineda-Pardo et al., 2019; Dileone, Mordillo-Mateos, Oliviero, & Foffani, 2018). The application of tSMS for 30 min is a safe procedure (Oliviero et al., 2015).

Neuronavigation Procedure

For both experiments, we used neuronavigation using standardized stereotaxic space and frameless stereotaxy (BrainSight, Rogue Research) with a Polaris infrared tracking system (NorthernDigital) to measure the anatomical landmarks on each participant's head. A high-resolution MRI was obtained from participants (T1-weighted images, fast spoiled gradient-echo with repletion time of 11.9 msec, echo time of 5 msec, flip angle of 40 mm, slice thickness of 1 mm, matrix size of 256) and transformed into standardized stereotaxic space. The coordinates selected for SMA ($x = -6, y = -6, z = 63$) were obtained from a previous neuroimaging study investigating automatic cognitive control (Albares et al., 2014). Yet, the stimulation effects of both NIBS techniques are not specific to the left or right hemisphere when placed close to the midline. The Talairach coordinates were converted into each participant's native MRI space using the reverse native-to-Talairach transformation.

Statistical Analysis

For the training phase of the go/no-go learning task, GoRTs mean and variance as well as p(respond|no-go) were separately entered in a three-way ANOVA with Treatment (rTMS, tSMS) as between-subjects factor, Condition (real, sham), and Blocks (1–6) as within-subject factors. For the test phase, a four-way ANOVA with Treatment (rTMS, tSMS), Condition (real, sham), Stimuli (old, new), and Blocks (1–3) was used. A filter on GoRTs was applied to exclude responses larger than 850 msec on correct go trials. Post hoc comparisons were performed with Bonferroni-corrected Fisher's least significance difference tests.

To exclude possible order effects across sessions, a two-way ANOVA in the training phase of the go/no-go task was done with Session Order (first, second) as between-subjects factor and Block (1–6) as within-subject factor. Similarly, a three-way ANOVA in the test phase with Session Order (first, second), Stimuli (old, new), and Block (1–3) was performed. Given that NIBS techniques may be biased by subject cognitive capacities (subject-dependent effects; Arciniega, Gözenman, Jones, Stephens, & Berryhill, 2018), an additional analysis was performed to control for good versus bad inhibitors (behavior from sham sessions on the SST based on SSRT median split). A three-way ANOVA was then performed with Inhibitors (good, bad) as between-subjects factor, and Condition (real, sham) and Blocks (1–6) as within-subject factors in the training phase. Similarly, a four-way ANOVA with Inhibitors (good, bad), Condition (real, sham), Stimuli (old, new), and Blocks (1–3) was done for the test phase. Finally, to confirm task-related effects were modulated, we selected only those participants showing higher RT costs in the old compared with the new stimuli in the test phase (obtained from the first block).

The main variables analyzed in the SST were probability of inhibition, GoRTs, StopRespond RTs, SSD, and SSRTs using a two-way ANOVA with Treatment as between-subjects (rTMS, tSMS) and Condition (real, sham) as within-subject factors. Support for the null hypothesis (i.e., "evidence of absence") was sought with Bayesian paired t tests (as implemented in JASP) for negative findings. We compared real versus sham on the variable of interest, using default effect size priors (Cauchy scale 0.707). Results are reported using the one-tailed Bayes factor (BF; e.g., BF_{+0} represents $p(data|H_+)/p(data|H_0)$). We also provide the frequentist sensitivity (in terms of minimum effect size that the test would be able to detect with 80% power at 0.05 significance with the available sample size) of each test in which we applied the BF. Specifically, the minimum effect size (Cohen's d) that a frequentist paired t test would be able to detect with 80% power at 0.05 significance level is $d = 0.43$ with $n = 45$ (all participants), $d = 0.66$ with $n = 20$ (task effects), $d = 0.72$ with $n = 17$ (only rTMS participants), and $d = 0.55$ with $n = 28$ (only tSMS participants). Data were analyzed with SPSS 20 and JASP (JASP Team, 2021).

RESULTS

Go/No-Go Learning Task

As detailed below, no relevant impact of treatment (rTMS, tSMS) or condition (real, sham) was seen in the training or test phases. We first confirmed that the learning on the training phase was comparable between treatments (rTMS, tSMS) and conditions (real, sham). In the training phase, mean GoRTs were progressively shorter, as expected, from Block 1 (394.3 ± 8.8 msec) to Block 6 (361.1 ± 8.2 msec; $p < .001$; blocks: $F(5, 215) = 23.12$, $p < .001$; Figure 2) revealing a general improvement over practice, with no impact of treatment, $F(1, 43) = 1.74$, $p = .19$, or condition, $F(1, 43) = 0.77$, $p = .38$. A similar analysis showed a reduction of variability from Block 1 (6142.9 ± 937.9) to Block 2 (3192.5 ± 541.9, $p = .004$) and Block 4 (3667.5 ± 679.0, $p = .015$; blocks: $F(5, 215) = 4.93$, $p < .001$), with no impact of treatment, $F(1, 43) = 0.87$, $p = .35$, or condition, $F(1, 43) = 0.60$, $p = .44$. Meanwhile, p(respond|no-go) revealed improved performance with practice from Block 1 (2.2 ± 0.3%) to Block 2 (1.1 ± 0.2%, $p = .01$; blocks: $F(5, 215) = 2.53$, $p = .030$; Figure 2). Unexpectedly, p(respond|no-go) was higher before real stimulation (2.1 ± 0.2%) than before sham stimulation (1.5 ± 0.2; condition: $F(1, 43) = 6.18$, $p = .017$. Moreover, p(respond|no-go) was higher in participants receiving TMS stimulation (2.3 ± 0.3%) compared with participants receiving tSMS (1.2 ± 0.2%; treatment: $F(1, 43) = 6.04$, $p = .018$). These results indicate that the initial training performance was comparable across the different conditions of our experiment despite some slight differences in p(respond|no-go) variable.

We then examined the effect of SMA stimulation on automatic cognitive control (i.e., reversal of associations). In the test phase (results summarized in Table 1), mean GoRT showed a significant decrease from Block 1 (388.9 ±

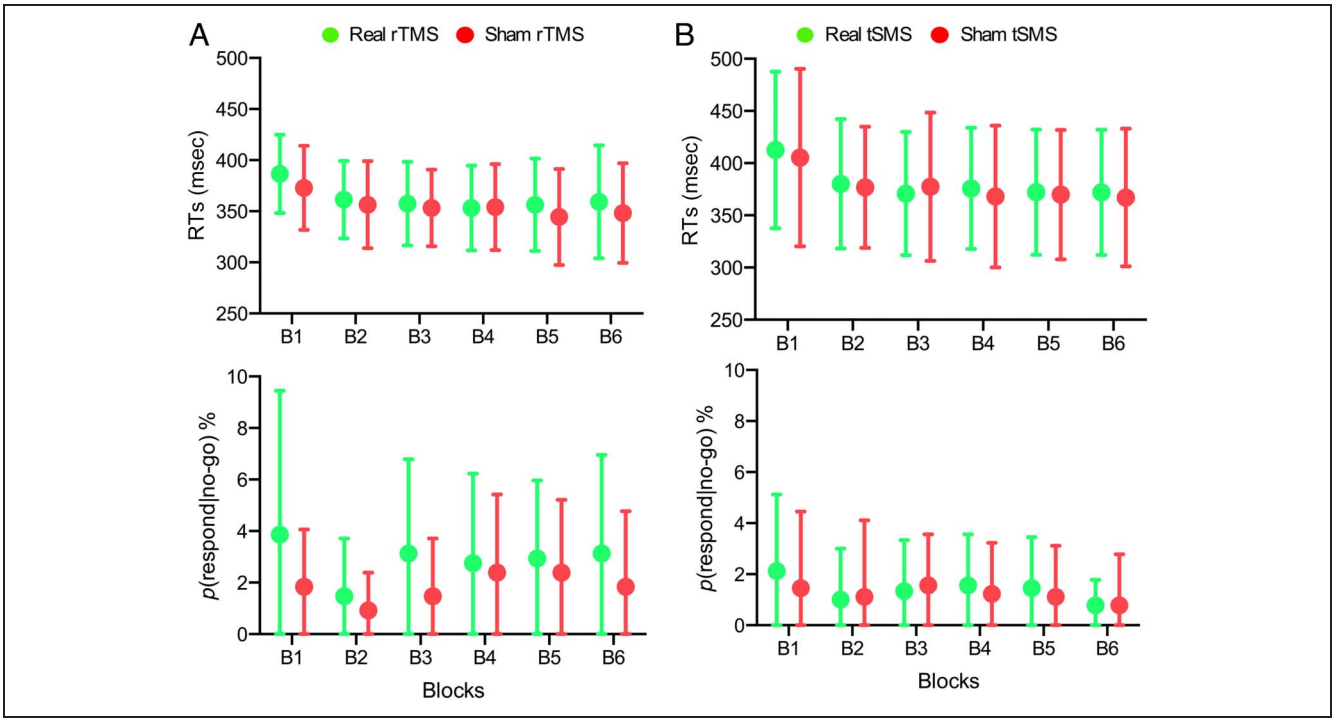

Figure 2. Training results in the go/no-go learning task by stimulation technique. (A) Average speed for go associations and probability of responding to no-go associations across blocks (mean and *SD*) for rTMS; (B) average speed for go associations and probability of responding to no-go associations across blocks (mean and *SD*) for tSMS.

Table 1. Overview of the Global Analyses of the Test Phase in the Go/No-Go Task

	GoRTs Mean		*GoRTs Variability*		*p(respond|no-go)*	
Variable	*F*	*p Value*	*F*	*p Value*	*F*	*p Value*
Treatment	0.07	.79	0.33	.56	8.93	< .01*
Condition	0.67	.41	1.88	.17	0.15	.69
Stimuli	1.25	.26	5	.031*	0.88	.76
Blocks	21.66	< .001**	10.41	< .001**	14.14	< .001**
Treatment × Condition	0.94	.33	2.33	.13	0.61	.43
Treatment × Stimuli	0.05	.82	0.43	.51	2.39	.12
Treatment × Blocks	0.77	.46	0.08	.92	4.60	.01*
Condition × Stimuli	0.13	.71	0.08	.76	1.33	.25
Condition × Blocks	2.03	.13	1.23	.29	1.65	.19
Stimuli × Blocks	0.11	.89	0.09	.91	0.53	.58
Treatment × Condition × Stimuli	0.26	.87	0.03	.86	1.56	.21
Treatment × Condition × Blocks	1.11	.33	2.28	.10	0.77	.46
Treatment × Stimuli × Blocks	0.33	.71	0.07	.92	1.86	.16
Condition × Stimuli × Blocks	0.36	.69	0.95	.38	0.67	.51
Treatment × Condition × Stimuli × Blocks	0.05	.94	0.83	.43	0.67	.51

* Statistical effects at values lower than .05.

** Statistical effects at values lower than .001.

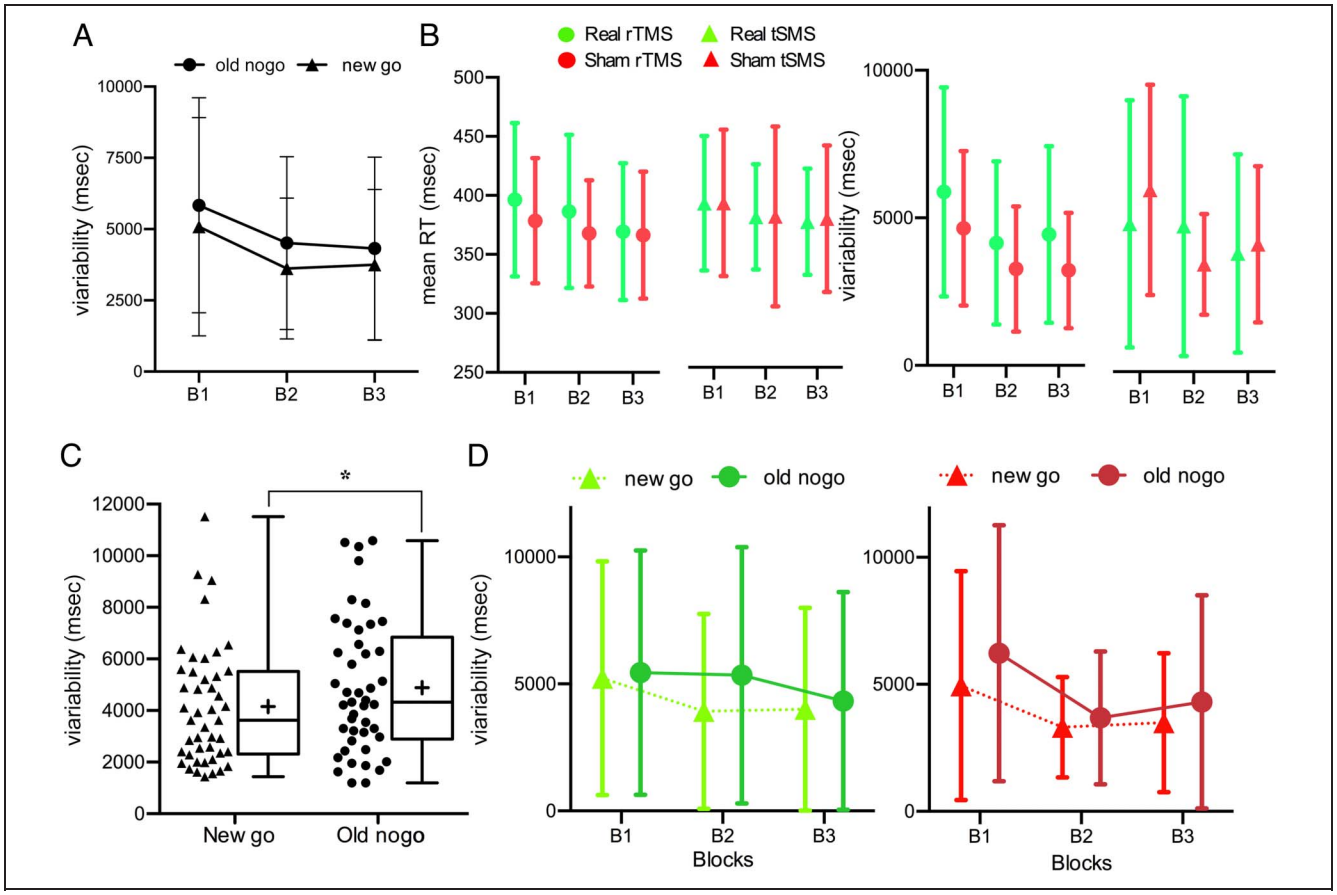

Figure 3. Reversal test results. (A) Effect of stimuli in response variability across blocks, (B) blocks effects across treatment and condition (for both stimuli categories) for mean and variability measures; (C) effect of stimuli in response variability (median, mean [+], min–max, and individual datapoints); (D) left, real stimulation group: variability for new associations (new go) and reversed associations (old no-go) across test blocks; right, sham stimulation group: variability speed for new associations (new go) and reversed associations (old no-go) across test blocks.

8.3) to Block 2 (378.0 ± 8.2, $p < .001$) and Block 3 (371.8 ± 7.5, $p < .001$; blocks: $F(2, 86) = 21.66$, $p < .001$; Figure 3B). No other significant main effects or interactions were observed, $F(2, 86) < 2.03$, $p > .13$. Similarly, GoRT variability was progressively reduced from Block 1 (5421.8 ± 485.8) to Block 2 (3994.1 ± 380.9, $p = .001$) and Block 3 (3993.1 ± 340.1, $p = .001$; blocks: $F(2, 86) = 10.41$, $p < .001$; Figure 3B). We also found that participants showed more variability when old stimuli were presented (4888.0 ± 388.7) compared with new ones (4150.3 ± 344.9; stimuli: $F(1, 43) = 5.00$, $p = .031$; Figure 3C), suggesting that previous no-go associations produced larger detrimental effects on adaptive behavior (consistent with 4). No other significant main effects or interactions were observed, $F(1, 43) < 2.33$, $p > .13$. Ultimately, prepotent responses were evident as shown by faster average no-go incorrect RTs (352.3 ± 80.3 msec) compared with go RTs (380.1 ± 59.5 msec; $t(41) = 4.12$, $p < .001$).

Finally, regarding accuracy levels, the p(respond|no-go) was gradually lower from Block 1 (3.9 ± 0.4) to Block 2 (2.4 ± 0.3, $p = .008$) and Block 3 (1.8 ± 02, $p < .001$; blocks: $F(2, 86) = 14.14$, $p < .001$). Similar to the training phase, we found that p(respond|no-go) was higher in participants receiving TMS stimulation (3.5 ± 0.3%) compared with participants receiving tSMS (2 ± 0.3%); Treatment: $F(1, 43) = 8.93$, $p = .005$. This difference was also expressed through a significant interaction between Treatment and Blocks for which p(respond|no-go) in Block 1 was higher in participants receiving TMS stimulation (3.4 ± 0.6%) compared with participants receiving tSMS (2.5 ± 0.5% $p = .001$; Treatment × Blocks: $F(2, 43) = 4.60$, $p = .013$). Given that also in the training phase rTMS participants showed an higher level in p(respond|no-go), we attributed this differences to a sample effect rather than a treatment or task effect. No other significant main effects or interactions were found, $F(1, 43) < 2.39$, $p > .12$. Importantly, none of the main variables showed interaction between condition (real, sham) and stimuli (old, new), suggesting SMA stimulation did not influence task performance (Figure 3D).

To disambiguate between absence of evidence and evidence of absence, we applied Bayesian statistics. The difference between old and new stimuli pooled across the three blocks in the testing phase was not smaller after real compared with sham stimulation (real < sham), using either mean RT ($BF_{-0} = 0.216$) or variability RT ($BF_{-0} =$

Table 2. Overview of Results of the SST

	Probability of Inhibition		*GoRTs*		*StopRespond RTs*		*SSD*		*SSRTs*	
Variable	*F*	*p Value*	*F*	*p Value*	*F*	*p Value*	*F*	*p Value*	*F*	*p Value*
Treatment	2.03	.16	1.14	.29	0.86	.77	2.24.	.14	0.08	.77
Condition	1.48	.23	0.93	.34	0.15	.69	1.24	.27	0.15	.69
Treatment × Condition	0.94	.33	0.10	.75	0.36	.85	0.41	.52	0.03	.85

0.201), thus providing moderate evidence that automatic inhibition was not decreased by SMA stimulation.

Stop Signal Task

A summary of the main behavioral results is summarized in Table 2. Probability of inhibition did not reveal significant differences between real and sham conditions (Condition: $F(1, 38) = 1.4, p = .23$). No significant effect of Condition was seen on initiation times (GoRTs; Condition: $F(1, 38) = 1.14, p = .29$; Figure 4A) and on StopRespond RTs (condition: $F(1, 38) = 0.15, p = .69$). As expected, SSD values (Condition: $F(1, 38) = 2.24, p = .14$) and SSRTs were similar between sham and real stimulation (Condition: $F(1, 38) = 1.74, p = .19$; Figure 4B). Likewise, no differences were found between TMS and tSMS groups.

Evidence of absence was confirmed by Bayesian statistics. Specifically, we obtained moderate-to-strong evidence that SSRTs did not increase (i.e., voluntary inhibition was not impaired) after SMA stimulation (real > sham; $BF_{+0} = 0.101$).

Task Effects

In 20 participants who exhibited the expected go/no-go task-related effects (i.e., slowing upon reversal of no-go associations), none of the main variables (mean GoRT, variability GoRT, and accuracy) showed a main effect of Condition (real, sham) or Condition × Stimuli (old, new) interaction, $F(1, 19) < 0.79, p > .38$.

Bayesian analysis confirmed that the difference of mean RT between old and new stimuli pooled across the three blocks in the testing phase was not smaller after real compared with sham stimulation (real < sham; $BF_{-0} = 0.181$). We hence provide moderate evidence that automatic inhibition was not decreased by SMA stimulation.

Participant-dependent Effects

Based on the SST results in the sham condition, we classified as good ($n = 20$) and bad ($n = 19$) inhibitors corresponding to median SSRT (192.6 msec) among all participants. None of the analyzed variables on the go/no-go task showed any interaction between Inhibitors and stimuli, suggesting that SMA stimulation was not biased by participant-dependent effects, $F(1, 37) < 2.75, p > .10$.

Session Order Effects

Because of the within-subject nature of the study, we verified whether session order had any possible impact on the null findings on the go/no-go task. No main effects or interactions were found for Session Order (first, second) with the main factors, $F(1, 43) < 1.26, p > .29$. Hence, our results were not biased by order.

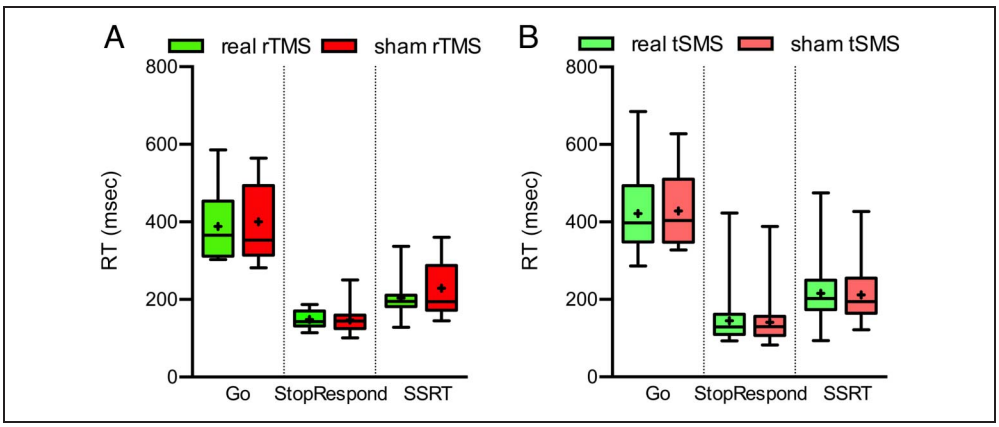

Figure 4. Stop signal results, showing speed of initiation (go trials), failed stop trials (stop respond trials) and SSRT values (median, mean [+], and min–max) for (A) rTMS and (B) tSMS. (A) Speed of initiation (go trials), failed stop trials (stop respond trials) and SSRT values (mean and *SD*) for rTMS (B) speed of initiation (go trials), failed stop trials (stop respond trials), and SSRT values (mean and *SD*) for tSMS.

DISCUSSION

Automatic control was achieved after learning inhibitory associations, as shown by larger variability costs when reversing no-go associations (consistent with Verbruggen & Logan, 2009). However, neither automatic (go/no-go learning task) nor voluntary inhibition (SST) was modulated by two NIBS techniques over the SMA. The results are compatible with the hypothesis of a reduced or indirect involvement of SMA in automatic control of behavior. Alternatively, we discuss possible compensatory options that after SMA stimulation could have taken control of the automatic behavior.

Some methodological concerns shall be initially considered. Given the moderate evidence toward the null hypothesis, using additional tasks that could respond to our NIBS procedures would have more strongly supported the negative findings. Our use of the SST was based on the idea that more anterior sections (i.e., pre-SMA) are in charge of goal-directed inhibition and, as expected, neuromodulation did not change this behavior. Alternatively, one could have included the stimulation of alternative cortical areas that participate in automatic control to provide evidence of neuromodulation effects. Yet, although this option is in general of value, the use of sham versus active stimulation represents a valid option to compare specific stimulation effects over the behavior of interest. In a similar vein, having neuroimaging data after participants received stimulation would have been highly informative on the state of SMA during automatic cognitive control. This may be a future methodological option in new studies. Another methodological constraint is the number of training sessions to reach automaticity. Because stopping associations were not altered by NIBS, our results may indicate that the behavior was not fully automated in our participants. This would imply the need of adopting longer protocols in future experiments. However, in our case, we used a reversal test condition that revealed larger variability costs for the practiced condition, which denotes automaticity. Yet, alternative methods in the field of habitual behavior are being largely discussed to include longer training sessions (Watson & de Wit, 2018) or using implicit association learning (rather than explicit instructions as used here) to infer when and where reward is given, to induce greater dopaminergic firing and reinforcement learning mechanisms (Coddington & Dudman, 2019). Moreover, our NIBS protocols are not spatially specific for effects to either left or right SMA. The spatial delimitation of our NIBS protocols could have modulated both SMA hemispheres, or anterior sections including pre-SMA that would bias the anatomo-functional link of our findings. Yet, unilateral lesions of the SMA proper in previous studies did not induce significant effects on learning new sequences and left unimpaired, previously well-learned sequences (Nakamura, Sakai, & Hikosaka, 1999). Possibly, interfering with bilateral SMA using unspecific NIBS techniques have different effects compared with focal unilateral lesions. For these reasons, our negative findings require future testing and replication to be confirmed.

Our study was motivated by understanding the neuromodulation effects of SMA associated to automatic components of cognitive control. Second, we aimed to test SMA involvement over voluntary control, associated to anterior sections of SMA complex (i.e., pre-SMA; Aron et al., 2007) to confirm expected null effects after stimulation. Previous neuroimaging accounts link SMA to automated control, planning, and response selection (Hirose, Nambu, & Naito, 2018; Albares et al., 2014; Smittenaar et al., 2013). While the SMA role in adaptive behavior is not questioned here, a possible reframing of inessential or distributed controlling processes may be plausible based on our findings. Our lack of significant findings using two inhibitory NIBS over the SMA may entail two possibilities: either interrelated SMA functions were used or an alternative bottom–up route was exploited to generate automatic programs (via compensatory mechanisms).

Cognitive control involves several executive operations including cue detection, conflict resolution, switching between behavioral options or the ability to wait, all functions linked to SMA hub, and other prefrontal regions (Watanabe et al., 2015; Herz et al., 2014; Oehrn et al., 2014; Vallesi et al., 2009; Forstmann et al., 2008; Nachev et al., 2008; Isoda & Hikosaka, 2007; Rushworth et al., 2004). Specifically, the flexible function of SMA plays a dominant role in rule and task sets (Forstmann et al., 2008, 2010; Vallesi et al., 2009; Nachev et al., 2008; Rushworth et al., 2004) and is important for contextual adaptation, motor planning, stimulus-triggered responses, or selective inhibition (Albares et al., 2014; Obeso et al., 2013; Smittenaar et al., 2013; Nachev et al., 2008). Importantly, these functions are all essential to integrate and learn how to successfully adapt in unexpected contexts that with repetition will build upon automatic control sources (Smittenaar et al., 2013; Ridderinkhof et al., 2004; Shiffrin & Schneider, 1984). Previous imaging findings reveals increased activity over putamen, SMA, and the subthalamic nucleus in response to predicted and unpredicted stop trials (Smittenaar et al., 2013), acting as a controlling system in stable contexts to selectively engage expected actions. Given an expected event, behavioral outputs require switching from controlled to automatic processing based on the available contextual information (Isoda & Hikosaka, 2007). This reversing mechanism is thought to rely on SMA and other regions (Wang, Mamelak, Adolphs, & Rutishauser, 2019; Isoda & Hikosaka, 2008, 2011) by engaging local inhibitory gabaergic circuitry (Boy et al., 2010). Possibly, SMA activity previously reported (Albares et al., 2014; Smittenaar et al., 2013) may be driven by embodying contextual rules with varying complexity to activate programs of initiation, switching, or inhibition to either controlled or automatic processes.

Based on the above, we suggest SMA activity reported in imaging studies was inessential to automated control

mechanisms. Rather, it may relate to selection and planning of adapted actions enabled by anticipatory cue presentation. After interfering with SMA functionality, automated associations learned beforehand were possibly favored to gate controlled and goal-directed systems. Hence, SMA controlling function was possibly biased to gate behavior toward the attentive controlled system, and thus, no changes were seen in automated variables in our task (whereas a larger effect on variability was found for inhibitory associated images). In fact, our task design did include comparisons between new and old items and in pure forms of goal-directed inhibition (the SST), without impairments in both forms of goal-directed control.

A second interpretation stems from neurophysiological and connectivity evidence that supports bottom–up recruitment in absence of adequate SMA activity. Lost SMA recruitment and its associated functions in adaptive contexts may have boosted interconnected regions via compensatory mechanisms. In fact, previous studies report distant neural changes after NIBS (Ruff et al., 2006) and, following tSMS over the SMA, functional connectivity engaged significantly the right IFG, associated to slower response planning (Pineda-Pardo et al., 2019). Indeed, earlier signals in IFG (~160 msec; Jana, Hannah, Muralidharan, & Aron, 2020) precede those in SMA when stopping actions (170 msec; Albares et al., 2014) and thus could take over automatic control by enforcing active goal-directed mechanisms. This view agrees with a prior result were an increase in right IFG activity was independent of associations between stimuli and stopping, suggesting a bottom–up automatic control mechanism (Lenartowicz et al., 2011). Hence, the nonessential contribution of SMA suggested in our results may be undertaken by interrelated cognitive control hubs.

Overall, our experiments found no evidence of an effect of SMA modulation over automatic cognitive control. We shall interpret these findings with caution as further neuromodulation options shall be tested. Our negative findings questions previous neuroimaging patterns of SMA activity during automated control of behavior that may possibly explain key interrelated processes. Future studies should assess the causal relationship between SMA and automatic control.

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Data Statement Availability

Data and code have been made available via https://osf.io/46pbq/.

Author Contributions

Pasqualina Guida: Data curation; Formal analysis; Writing—Original draft. Guglielmo Foffani: Methodology; Supervision; Writing—Review & editing. Ignacio Obeso: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Supervision; Writing—Original draft; Writing—Review & editing.

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Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

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