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The causal role of DLPFC top-down control on the acquisition and the automatic expression of implicit learning: State of the art

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ABSTRACT

Implicit learning refers to the incidental acquisition and expression of knowledge that is not accompanied by full awareness of its contents. Implicit sequence learning (ISL) represents one of the most useful paradigms to investigate these processes. In this paradigm, participants are usually instructed to respond to the location of a target that moves regularly through a set of possible locations. Although participants are not informed about the existence of a sequence, they eventually learn it implicitly, as attested by the costs observed when this sequence is violated in a reduced set of control trials. Interestingly, the expression of this learning decreases immediately after a control trial, in a way that resembles the adjustments triggered in response to incongruent trials in interference tasks. These effects have been attributed to a control network involving dorsolateral prefrontal cortex (DLPFC) and cingulate (ACC) structures. In the present work, we reviewed a group of recent studies which had inhibited DLPFC top-down control by means of non-invasive brain stimulation to increase the *acquisition* of ISL. In addition, as no previous study has investigated the effect of inhibiting top-down control on releasing the automatic *expression* of ISL, we present a pre-registered – yet exploratory – study in which an inhibitory continuous theta burst stimulation protocol was applied over an anterior-ventral portion of the dorsolateral prefrontal cortex (DLPFC) highly interconnected with the ACC, and whose activity has been specifically linked to motor control (i.e., Right DLPFC, n = 10 or the Left DLPFC, n = 10), compared to active Vertex stimulation (n = 10). Contrary to our hypotheses, the results did not show evidence for the involvement of such region in the expression of

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ISL. We discussed the results in the context of the set of contradictory findings reported in the systematic review.

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1. Introduction

1.1. *Implicit learning*

The common sense we have about memory derives from our ability to encode and retrieve explicit information on the facts and events occurring around us. Nevertheless, alongside with its explicit, declarative counterpart, implicit memory supports a great part of our daily interactions with the environment and comes into play from when we simply lace our shoes to when we perform a difficult piano sonata. The process leading to the acquisition of these types of skills, which requires (proportionally) extended practice, but then unfolds automatically in the appropriate context, has been termed implicit learning. In laboratory experiments, implicit learning has been operationalized as the incidental acquisition of structured information, whose contents escape full awareness, but nevertheless influence performance, mainly in terms of response facilitation to the learned structure (Reber, 1993, 2008). Thus, besides being incidental (i.e., no instructions on the existence of a structure are provided to the participants beforehand), this learning is defined as implicit, as participants' performance cannot be explained in terms of their explicit knowledge, as measured after learning has taken place (Jiménez, Méndez, & Cleeremans, 1996; Reed & Johnson, 1994).

One of the paradigms used to study implicit learning is implicit sequence learning (ISL) (Nissen & Bullemer, 1987), in which the knowledge contents concern statistical regularities that participants automatically extract from the sequential presentation of stimuli during a covert task. These statistical regularities may have a perceptual (e.g., a sequence of stimulus characteristics, such as shapes, colors, or locations), a motor (e.g., a sequence of responses), or an abstract nature (e.g., a sequence of tasks) (Abrahamse, Jiménez, Verwey, & Clegg, 2010), and consequently, different tasks have been used to tap into them.

In particular, since its first introduction by Nissen and Bullemer (1987), the Serial Reaction Time (SRT) task has been considered as the canonical task to investigate ISL. In this four-choice reaction time task, participants are simply instructed to localize the position of a target appearing on each trial over one of four possible positions on the screen and press the corresponding key. Unbeknownst to the participants, on the majority of the trials, the target appearance follows a series of locations, and therefore responses, conforming to a sequence (i.e., training sequence), which gets violated by less frequent transitions (i.e., control sequence) on a reduced set of trials.

Interestingly, complex sequences, such as second order conditional (SOC) structures, allow the probabilistic presentation of either the training or the control sequence on a trial-by-trial basis, and further support the implicitness of the learning process (Jiménez et al., 1996; Reed & Johnson, 1994; Schvaneveldt & Gomez, 1998). Fig. 1 shows an example of two SOC sequences: as can be observed, the presentation of the target on a given location (e.g., 4th) conforms to either the training or the control sequence depending on the previous two locations. With SOC structures, participants become increasingly faster across training with those third items in a triplet of positions conforming to the training sequence (i.e., training trials, from here on), and increasingly more inaccurate with those conforming to the control sequence (i.e., control trials, from here on) – thus, ISL is acquired (Jiménez et al., 1996).

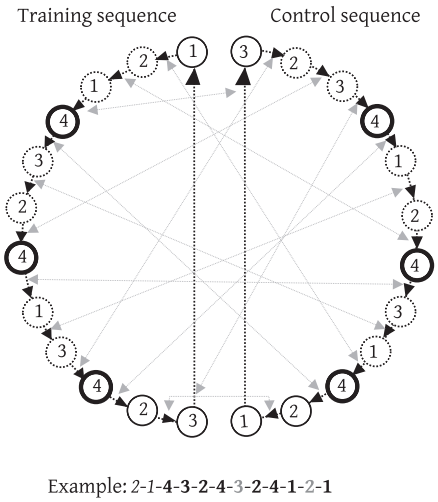

Fig. 1 – The two semicircles represent the training (e.g., 80% trials) and the control (e.g., 20% trials) sequences. These are second order conditional structures (SOC), because a target appearing on the 4th location on the screen (bold circles) can be classified as training or control only based on the context created by the previous two locations (dotted circles). For example, if the 4th location (trial n) is preceded by the 1st (trial n-1) and by the 2nd location (trial n-2), it is a training trial, if it is preceded by the 1st (trial n-1) and by the 3rd location (trial n-2), it is a control trial. The black arrows represent the transitions allowed within each sequence; the light grey arrows describe the possible transitions between sequences. The example below shows a series of possible transitions from training (in bold black) to control (in bold grey) locations across ten trials. The first two locations at the beginning of each block (in italic) cannot be properly classified but create the appropriate context for the following trials.

1.2. *Automatic implicit sequence learning: the need for control*

The automatic unfolding of routines represents a huge advantage in terms of time and resources, as these can be dedicated to other simultaneous actions or thoughts. At the same time, a rigid and uncontrolled deployment of automatic behavior is at odds with a constantly changing environment demanding for behavioral and cognitive flexibility (i.e., cognitive control). As such, the distinction between automatic and controlled operations, rather than being net in practice, would represent the extremes of a continuum on which a process is situated depending on both learning and context, the latter reflecting the concurrent processing ongoing in the system at a given time point (Cohen, 2017). Several sources of mostly behavioral evidence suggest that also the cognitive pattern of ISL would be rearranged on that continuum, and that the engagement in top-down cognitive control processes would selectively reduce the automatic expression of ISL.

1.2.1. *Behavioral evidence*

In a series of experiments, Vaquero, Lupiáñez, and Jiménez (2019) trained participants under different conditions, and then transferred them to either a more or less control demanding context. Results showed that expression of ISL was selectively disrupted when transfer occurred towards a more control-demanding context, as when participants were first trained with the standard SRT task (i.e., single target) and then responded to the same target, but surrounded by distracters (see also Experiments 2 and 3 in Jiménez, Vaquero, & Lupiáñez, 2006). On the contrary, expression of ISL remained solid when transferred from learning with a target surrounded by distracters to a context with a single target, thus highlighting that not every context change affects learning equally.

Moreover, new data demonstrated that the expression of ISL might be modulated by more punctual changes within the sequential structure, as the trial-by-trial context conveyed by the transitions from one SOC structure to the other (Jiménez, Lupiáñez, & Vaquero, 2009; Prutean et al., 2020). Using a version of the probabilistic sequence learning task that included 10% of individual trials generated according to the control sequence, among 90% of trials generated according to the training sequence, Jiménez et al. (2009) showed that learning improved steadily with training, and that when it was established, its expression decreased selectively after a control trial. This effect resembles the congruency sequence effect (CSE) that is commonly observed in classic interference tasks (Braem, Abrahamse, Duthoo, & Notebaert, 2014; Duthoo, Abrahamse, Braem, Boehler, & Notebaert, 2014; Gratton, Coles, & Donchin, 1992), where the difference in response time (RTs) between incongruent and congruent trials is mostly shown after congruent trials, but decreases after incongruent ones. Akin to this literature, Jiménez et al. (2009) interpreted the observed CSE in ISL as an index of reactive cognitive control, as predicted by the influential conflict monitoring account (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Miller & Cohen, 2001). According to Jiménez et al. (2009), the presentation of a reduced set of control trials violated participants' implicit predictions on the stimulus position (i.e., conforming to the expected training sequence) and set off conflict (see also Verguts & Notebaert, 2009), which in turn triggered a transient increase in cognitive control (Botvinick et al., 1999, 2001) and therefore reduced the automatic expression of ISL on the following trial. Follow up studies replicated the CSE in both motor and perceptual ISL, as well as with less complex structures (i.e., FOC, first order conditional structures, as in D'Angelo, Jiménez, Milliken, & Lupiáñez, 2013). Moreover, through a series of experiments, we determined under which circumstances the CSE observed in the expression of ISL could be safely taken as an index of the engagement of transient cognitive control (cfr. revised-CSE in Prutean et al., 2020), rather than a result of simple associative learning mechanisms (Beesley, Jones, & Shanks, 2012).

Finally, we further combined the SRT task with the Oddball task and showed that the expression of ISL can be modulated by control-demanding manipulations which are orthogonal to either the SRT task or the sequence (Prutean et al., 2020). In the typical Oddball task (Parmentier, 2008, 2014, 2016), participants perform a simple discrimination task on trials containing a small proportion of stimuli that differ from the standard in a task-irrelevant feature. The results of these experiments suggest that the violation of the expectations induced by such oddball stimuli produces an effect akin to the recruitment of cognitive control. Thus, in one of our experiments (i.e., Experiment 3 in Prutean et al., 2020), we trained participants with a standard SRT task where all trials were preceded by a task-irrelevant standard 600 Hz sound. Then, during some transfer blocks, an oddball white noise sound violated the standard sound regularity, and, critically, hindered the expression of ISL, resulting in an effect analogous to the CSE (cfr. oddball-dependent sequence effect in Prutean et al., 2020). We suggested that, as for the CSE, the oddball-dependent sequence effect was governed by the same control mechanisms that were triggered after conflict detection – an interpretation which is also compatible with the electrophysiological evidence of attentional reallocation on task-relevant dimensions after oddball distraction (Berti, 2008).

Taken together, we surmise that up-to-date cumulative behavioral evidence suggests that engagement in cognitive control reduces the automatic expression of ISL.

1.2.2. *Neural evidence*

As discussed so far, the behavioral evidence on how cognitive control inhibits the expression of automatic ISL can be explained by the cognitive processes implicated in the conflict monitoring account (Botvinick et al., 2001; but see, 1999; Banich, 2009) which, interestingly, has also put forward predictions on the possible neural basis of the conflict-control loop engaged in the CSE. This model suggests that, during task performance, task-relevant goals are held in the dorsolateral prefrontal cortex (DLPFC), which exerts top-down control on the brain regions involved in stimulus and response processing in order to enhance task-relevant information processing while inhibiting the effects of task-

irrelevant information, and to produce appropriate responses despite the impact of potentially inappropriate but over-learned response tendencies. However, given that optimal cognitive patterns are not entirely top-down driven, the dorsal anterior cingulate cortex (dACC) monitors for the interference arising from competing task-irrelevant information. The detection of this interference triggers conflict, which represents a signal for the DLPFC to exert more control over task-relevant brain regions and assist performance. The activation of the dACC-DLPFC loop results in a transient increase in cognitive control engagement which reduces conflict on the subsequent trial, thus leading to the observation of the CSE (i.e., conflict adaptation).

The evidence gathered to validate the neural bases of conflict adaptation is quite heterogeneous, but eventually converges on the involvement of either the right (Egner & Hirsch, 2005; Kerns et al., 2004) or the left DLPFC (Kerns, 2006) during the involvement of conflict-triggered cognitive control, at least in classic interference tasks. However, up to date we are not aware of any single study which has investigated the role of DLPFC during the CSE observed in ISL. Some studies have nevertheless more generally addressed the role of DLPFC during ISL, and may therefore provide some clues on the involvement of DLPFC in those trials in which an unexpected control trial replaces a sequence trial.

In the context of ISL, the emergence of a CSE is intrinsically related to the learning process, as both the congruency and the incongruency between the actual and the expected stimulus position develop throughout extensive training. For instance, across training with a probabilistic version of the SRT task, we would expect a gradual decrease in activity in control-related brain regions if stimuli were presented in an expected location, and a phasic increase in activity in the same regions following their appearance in an unexpected position. However, studies investigating DLPFC involvement in ISL through probabilistic versions of the SRT and SOC structures are missing as well, while those implementing a deterministic version of the SRT task have reported contradictory results. For example, Poldrack et al. (2005) noticed an initial increase in the right DLPFC activation during the initial performance of a deterministic SRT task under dual-task conditions, which then decreased with the development of performance automaticity. On the contrary, Seidler et al. (2005) observed an increase in the right DLPFC activity during the automatic expression of ISL. These controversial results could be due to the deterministic presentation of the sequential information, which are known to increase participants' explicit awareness of the structured material, and has been correlated with a recruitment of the prefrontal cortex, for its connections to the medial temporal structures involved in declarative memory processes (Destrebecqz et al., 2005).

1.3. *Controlled implicit sequence learning: the need for causality*

One way to disentangle the contrasting correlational evidence on the role of DLPFC in either the acquisition or expression of ISL would be to experimentally manipulate its recruitment by means of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) – which can provide true insights into causal relationships between the brain and cognition (Bikson et al., 2016; Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009; Rossini et al., 2015).

1.3.1. *Aim of the present work*

The aim of the present work was precisely to clarify the causal role of DLPFC top-down control in the modulation of implicit learning. First, as shown in the PRISMA Flowchart of Fig. 2, we performed a systematic review of the existing literature on the topic, highlighting seven relevant studies, which have all targeted the DLPFC by means of non-invasive brain stimulation (i.e., TMS or tDCS protocols) either before (offline) or during (online) implicit learning *acquisition* in healthy volunteers. Second, as none has modulated its activity after learning acquisition to tackle its role in the automatic *expression* of implicit learning – as the previous behavioural and neural evidences would suggest – we present a new study to precisely bridge this theoretical gap. The outcomes of the present experiment will be integrated into our review of the literature, in an attempt to depict the existing evidence on the causal role of DLPFC top-down control in modulating the acquisition or the automatic expression of implicit learning.

In the present study, we used a continuous theta burst stimulation (cTBS) approach (Nyffeler, Wurtz, Lüscher, et al., 2006; Nyffeler, Wurtz, Pflugshaupt, et al., 2006; Oberman, Edwards, Eldaief, & Pascual-Leone, 2011) to experimentally inhibit an anterior-ventral portion of the DLPFC highly interconnected with ACC during top-down motor control (Cieslik et a., 2012) and investigate its causal role – as part of a cognitive control network (Botvinick et al., 1999, 2001) – in releasing the automatic expression of ISL. Participants were first trained for a series of blocks with a probabilistic version of the SRT task conveying SOC information (Reed & Johnson, 1994; Schvaneveldt & Gomez, 1998). Then, we applied an inhibitory cTBS protocol on the left DLPFC, the right DLPFC, or the Vertex (as a control area), with the stimulation area being manipulated between participants. After the stimulation, participants performed again a series of blocks of trials in order to highlight between-group differences in performance, as well as the time course of the stimulation aftereffects. Considering the above-mentioned behavioral evidence on how cognitive control affects the expression of ISL in previous experiments with the same SRT task, we expected to observe an increase in the expression of ISL after the inhibition of either the left DLPFC, the right DLPFC or both, as compared to the control group (i.e., vertex stimulation). Indeed, given the heterogeneity of the literature supporting either right or left involvement of top-down control regions in conflict-related paradigms, and the scarce evidence on thier involvement in ISL paradigms, our aim was also to explore possible hemispheric asymmetries of DLPFC contributions to ISL expression. To further support our previous findings on the emergence of the CSE (Jiménez et al., 2009; Prutean et al., 2020), we sought to replicate the effect in the present experiment as well.

Note that the exploratory vein of this study, together with the hypotheses, the planned and exploratory analyses were

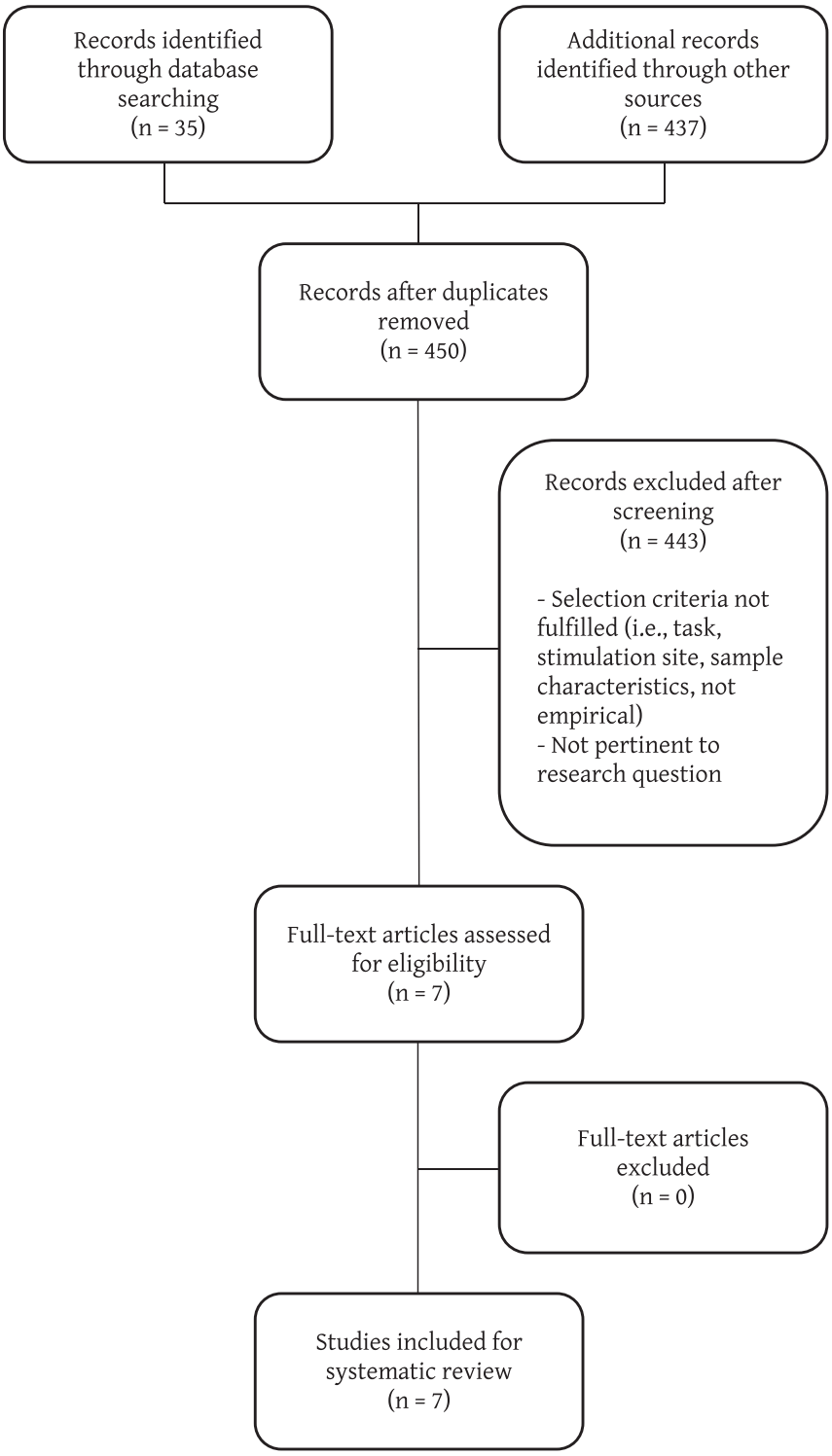

Fig. 2 – PRISMA flowchart of the systematic review.

preregistered with the pre-registration template from AsPredicted.org on Open Science Framework before data collection (osf.io/wbeuy). All deviations to the pre-registered procedures and analyses are transparently identified. In particular, we preregistered the sequential sampling of data based on gathered evidence (see "Goals and hypotheses of the current study", and "Participants" sections in the preregistration), albeit in a frequentist framework. Since this cumulative purpose is most appropriately framed in a Bayesian framework, we report the Byaesian analyses for the main effects of interest (i.e., the effect of stimulation on the expression of ISL and on CSE).

2. Methods

2.1. Systematic review

2.1.1. Operationalization of implicit learning

Consistent with current considerations on the representational basis of sequence learning (Abrahamse et al., 2010), we considered not only those tasks concerning either motor and/or perceptual sequence learning, such as the deterministic and probabilistic versions of the SRT task, or its variant, the Alternating Serial Reaction Time task (ASRT; Howard & Howard, 1997), but also tasks concerning more abstract forms of sequence representation, such as the Task Sequence Learning paradigm (TSL; Heuer, Schmidtke, & Kleinsorge, 2001).

The ASRT is also a four-choice reaction time task very similar to the SRT task, but where only the locations of the even trials are predetermined according to a fixed sequence, whereas the odd trials are completely random. Thus, the concatenation between random and fixed alternating trials make some runs of triplets (i.e., three positions in a row) more frequent than others, akin to the probabilistic version of the SRT task implementing SOC structures. Participants in this task seem to be able to pick up the statistical regularities arising from these sequences, and show faster responses across training to high frequency as compared to low frequency triplets.

As for the TSL paradigm, participants are presented with a stream of stimuli, with their identities or perceptual characteristics determining both the task to be performed and the specific response to be emitted. For example, participants may have to perform a numerical judgement (low *vs* high number) or a letter judgement (vowel *vs* consonant) depending on whether a digit or a letter is presented, and they may also need to produce a different mapping between stimuli and responses depending on other features of the stimuli (e.g., use a mapping when the target is red, and the opposite when it is green). Unbeknownst to the participants, the presentation of the four different task-mapping combinations conform to a repeating task sequence which is independent of the stimuli identities and the responses of the single tasks (outcomes). Even though the task-mapping combinations are also predicted by the stimuli characteristics instructing the task/mapping switch (e.g., the transition from a red number to a green letter), this perceptual information alone is not sufficient for ISL to occur, and participants acquire sequential information also at a more abstract level (i.e., a sequence of tasks), as demonstrated by the increase in RTs when it gets replaced by a different sequence or a random order of tasks (Weiermann, Cock, & Meier, 2011).

2.1.2. Literature search

We performed a systematic review on this literature following the recommendations of PRISMA (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009); see also Table S1 in Supplementary materials). A PRISMA Flowchart is shown in Fig. 2 which summarizes the steps of our literature search and selection (see also File S2 in Supplementary material for a detailed description of the search procedure). In particular, we first consulted the database of PubMed and Scopus using the search equation (implicit learning) AND (DLPFC) AND (TMS OR tDCS OR TBS). Then, a search of grey literature was conducted on Google Scholar using the search expressions *"implicit learning" "dlpfc" "tDCS|TMS|TBS"*. The latest search was carried out by N.P. in March 2020, without any time restriction.

2.1.3. Selection criteria

Further, we refined our search including only empirical studies (i) which had manipulated the recruitment of the DLPFC with non-invasive brain stimulation techniques, (ii) had investigated ISL through either the deterministic or probabilistic versions of the SRT task, the ASRT task, or TSL paradigm, (iii) recruiting healthy participants, and (iv) in which the active stimulation of the DLPFC was compared to a control condition (i.e., sham stimulation or control site).

2.2. Empirical study

2.2.1. Participants

The initial sample size for this study was calculated from the effect size of ISL ($\eta_p^2 = .356$) observed in a previous experiment (i.e., Experiment 3, in Prutean et al., 2020). A power analysis with G*power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009) revealed that at least six participants were necessary to observe such an effect with $1\text{-}\beta = .99$, $\alpha = .01$, and a correlation among repeated measures of .6. However, despite having increased the sample size to ten participants per group, the initial power analysis was not appropriate for a between groups comparison. Nonetheless, for the exploratory vein of the study, we pre-registered the possible increase of the initial sample size based on gathered evidence, and thus, more adequate Bayesian analyses complemented the main analyses of interest. Indeed, sequential hypothesis testing with Bayes Factors represents a valid approach to run exploratory experiments when the size of the effect is unknown and the final sample size is constrained for practical reasons (Schönbrodt, Wagenmakers, Zehetleitner, & Perugini, 2016; Schönbrodt & Wagenmakers, 2018; Stefan, Gronau, Schönbrodt, & Wagenmakers, 2019). The limitation of this approach will be further considered in the discussion. Hence, thirty healthy volunteers (ten per stimulation group; two left-handed), which had never participated in similar experiments before, took part in this experiment in exchange for 10 euros/hour, and they were randomly assigned to the Right DLPFC group ($n = 10$, 4 males, $M_{age} = 23.8$, $SD_{age} = 3.74$), the Left DLPFC group ($n = 10$, 6 males, $M_{age} = 24.00$, $SD_{age} = 4.19$) or the Vertex group ($n = 10$, 5 males, $M_{age} = 21.9°$, $SD_{age} = 1.52$). Prior to the experiment, participants were assessed for TMS/cTBS and magnetic resonance imaging (MRI) exclusion criteria (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group T. S. of T. C, 2009; Rossini et al., 2015) and, before each of the two sessions, they signed an informed consent which informed them on their freedom to withdraw from the study at any time, without penalty. The experiment was part of a larger research project approved by the Universidad de Granada Ethical Committee (175/CEIH/2017), and was concordant with the ethical standards of the 1964 Declaration of Helsinki.

2.2.2. *Apparatus and materials*

The sequence of stimuli composing the SRT task was presented on a 14-inch computer screen through the INQUISIT 4.0 software. On each trial, the stimulus could appear over one of four horizontal placeholders on the screen, and participants pressed one of four spatially mapped response keys on a QWERTY keyboard to localize it. The sequences used to present the targets were two SOC sequences (Schvaneveldt & Gomez, 1998), each composed by a series of twelve items: by representing the first, second, third, and forth position on the screen from left to right with digits 1, 2, 3, and 4, respectively, the series of locations 1-2-1-4-3-2-4-1-3-4-2-3 conformed to one structure (i.e., training sequence for half of the participants), and the series of positions 3-2-3-4-1-2-4-3-1-4-2-1 conformed to the other structure (i.e., control sequence for half of the participants; see Fig. 1 for examples of transitions within and between sequences).

2.2.3. *Procedure*

The whole experiment consisted in two experimental sessions: a first MRI session, lasting half an hour, in which each participant's T1-weighted anatomical MRI was acquired, and a second TMS session, lasting an hour and a half, during which participants performed the SRT task before and after receiving stimulation according to the corresponding stimulation group.

2.2.3.1. MRI SESSION. The structural MRI data were acquired from each participant through a 3T Siemens (MAGNETOM TrioTim) scanner at the Mind, Brain, and Behaviour Research Center (CIMCYC), University of Granada. T1-weighted anatomical magnetic resonance scans were acquired with a magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (repetition time, TR = 2530 msec; echo time, TE = 2.5 msec, slice thickness: 1 mm, field of view, FOV: 256 mm).

2.2.3.2. SERIAL REACTION TIME TASK. All the three groups performed the same SRT task before (prestimulation phase, blocks 1–12) and after the stimulation (poststimulation phase, blocks 1–6), followed by a final block of a cued generation task assessing the implicitness of sequence learning. During the SRT task, on each trial, an "X" letter appeared over one of four horizontal placeholders situated on the horizontal axis of the computer screen, and participants were instructed to localize its position by pressing the spatially correspondent Z, X, N, or M key on a QWERTY keyboard. Unbeknownst to the participants, the target transitions from one position to the other conformed to one sequence on 80% of the trials (i.e., training trials), and to the other sequence on the remaining 20% of the trials (i.e., control trials). The status of the two SOC structures as training or control sequences was counterbalanced across participants (see Fig. 1). Previous evidence combining the SRT and the Oddball paradigms (Prutean et al., 2020) have shown that the presence of alerting cues before the presentation of visual targets boosts the emergence of the CSE, as opposed to a similar experiment implementing the same sequence manipulation in the absence of preceding sounds (see Prutean et al., 2020 for a comparison). Hence, the alerting sound was presented in the present experiment as well: each trial started with a 600 Hz sine wave tone presented over 150 msec, which was followed, after an interval of 100 msec, by the visual "X" target, which remained on the screen until the participant responded. If the response was correct, it was followed by a 100 msec post-trial pause, and a new trial began. If they committed an error, a visual white flash feedback was presented, and the task was delayed for 500 msec, as a way to encourage response accuracy. Compared to previous experiments implementing the same sequence manipulation, in the present study participants were trained over a longer period, in order to provide an appropriate stable prestimulation baseline that could be contrasted to the poststimulation phase, to highlight any change in the expression of ISL.

Because of this extensive training period, it became particularly important to assess the implicitness of the resulting knowledge through a cued generation task (Cohen, Ivry, & Keele, 1990; Jiménez et al., 2006; D'Angelo et al., 2013; D'Angelo, Milliken, Jiménez, & Lupiáñez, 2013, 2014). During this task, participants were presented twice, without repetitions, with twelve pseudo-random triplet sequences taken from their trained sequence. During the first two trials of these triplets, participants had to detect the "X" target as they did during the SRT task, by pressing the keys corresponding to their location. On each third trial, however, four question marks appeared, instead of the successor, occupying the locations above each of the four placeholders, and the participants' task was to predict the natural successor of the series by pressing the corresponding key. The generated response was encoded as matching the training triplet (e.g., positions 1-2-1 in Fig. 1), the control triplet (e.g., positions 1-2-4 in Fig. 1), or as random (e.g., positions 1-2-3 or positions 1-2-2). The learning process is considered implicit if the indirect measure shows greater sensitivity to sequence knowledge (i.e., a significant difference between training *vs* control trials in RTs and accuracy in the SRT task) as compared to the direct assessment (i.e., a non-significant difference between training *vs* control trials in the amount of generated trials; see Reed & Johnson, 1994), because there is no reason to think that participants would use their explicit knowledge more poorly when directly asked to do so compared to when they are not (Jiménez et al., 1996; Reingold & Merikle, 1989).

2.2.3.3. TMS PROTOCOL. Before performing the SRT task, participants underwent the resting motor threshold (RMT) measurement in order to calculate the maximum stimulator output percentage (% MSO) for the cTBS protocol. The RMT was calculated by delivering increasing % MSO pulses over the primary motor cortex (M1) representing the contralateral first dorsal interosseous (FDI), until observing motor evoked potentials (MEP) larger than 50 mV in five out of ten consecutive trials (Rossi et al., 2009; Rossini et al., 2015). MEPs were recorded through electromyography (EMG) and snap surface electrodes (Natus Neurology) from the FDI contralateral to the cTBS stimulation side, for the Left and Right DLPFC groups, and contralateral to the dominant hand, for the Vertex group. Focal pulses for either the RMT

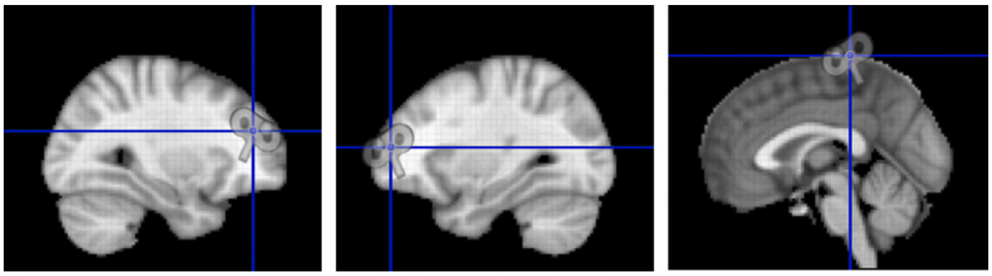

Fig. 3 – TMS stimulation coordinates of the three groups: from left to right, Right DLPFC (MNI centered in x = 30, y = 43, z = 23), Left DLPFC (MNI centered in x = −30, y = 53, z = 12), Vertex (MNI centered in x = 0, y = −34, z = 78).

measurement or the cTBS pulses were delivered though a 70-mm TMS figure-of-eight coil connected to a biphasic stimulator (Super Rapid 2, Magstim, Whitland UK) and held tangentially to the scalp at approximately 45° from the midline (Di Lazzaro et al., 1998).

After the training period with the SRT task, the cTBS protocol was applied. Three 30 Hz pulses were delivered every 200 msec for a total of 600 pulses in 33.3 sec at a % MSO equal to 80% of the RMT (Nyffeler, Wurtz, Lüscher et al., 2006; Nyffeler, Wurtz, Pflugshaupt et al., 2006). A direct comparison between this protocol and a very well established cTBS protocol (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) suggested that the first was significantly more effective in suppressing MEP amplitudes when applied to the motor cortex, even at the same (reduced) intensity as in Huang et al. (i.e., 80% active motor threshold, AMT) and with the same degree of M1 activation prior to the stimulation (Goldsworthy, Pitcher, & Ridding, 2012). The mean and standard deviation of the MSO percentage intensity used in the cTBS protocol were of $M_{\%MSO} = 46.93$, $SD_{\%MSO} = 2.48$ in the whole sample; $M_{\%MSO} = 47$, $SD_{\%MSO} = 2.83$ in the Right DLPFC group, $M_{\%MSO} = 47.1$, $SD_{\%MSO} = 6.26$ in the Left DLPFC group, and $M_{\%MSO} = 46.7$ $SD_{\%MSO} = 2.98$ in the Vertex group.[2] The scalp coordinates for the stimulation site were based on a previous study by Cieslik et al. (2012), who adopted a network-based approach to define the role of the DLPFC in executive motor control, especially in those situations demanding an increase in monitoring and cognitive control due to conflict following competition of response plans. In particular, the authors suggested that executive motor control was mostly carried out by the anterior-ventral part of the right DLPFC highly connected with its homologous in the left hemisphere, as well as with the ACC – a finding compatible with the prediction of the conflict monitoring account (Botvincik et al., 1999, 2001). Therefore, in accordance with these findings and as shown in Fig. 3, the MNI (Montreal Neurological Institute) coordinates of the two experimental groups were centered in x = 30, y = 43, z = 23 for the Right DLPFC group, and in x = −30, y = 53, z = 12 for the Left DLPFC group. The control stimulation site was the vertex, which was centered in MNI coordinates x = 0, y = −34, z = 78 (Heinen et al., 2011). Therefore, through the Brainsight Neuronavigation system (Brainsight, Rogue Systems, Montreal, Canada) we first normalized each individual MRI acquired during the first MRI session onto the MNI brain template, and then we localized the coordinates on the scalp of each participant. The stimulation (i.e., 33.3 sec duration) was manually controlled by the neuronavigation system, assuring the online maintenance of the relative position, orientation, and tilting of the coil with respect to the MNI coordinates and with an error inferior to 5 mm.

[2] Note that due to technical limitations, the stimulation intensity for this protocol could not exceed the 48% MSO of the machine. Thus, despite the fact that 11 participants required a more intense stimulation ($M_{\%MSO} = 55.33$, $SD_{\%MSO} = 3.35$ in six participants of the Right DLPFC group; $M_{\%MSO} = 57.12$, $SD_{\%MSO} = 3.33$ in the five participants of the Left DLPFC group), they received it at the maximum capacity of the machine (i.e., 48% MSO). Note that – however – this possible limitation was considered as potential source of variability in the latter analyses.

3. Results

3.1. Systematic review

As shown in the PRISMA flowchart in Fig. 2 (but see also File S2 in Supplementary materials), the search output from PubMed/Scopus (n = 35) and Google Scholar (n = 437) consisted in 472 initial records, further refined in 450 potentially interesting results after the removal of 22 duplicates. From these – based on an initial screening performed by N.P. – only 7 studies met our (i-iv) selection criteria. Their eligibility for the systematic review was further supported by the full-text assessment of other two independent reviewers (L.J., J.L.). The 7 studies fulfilling our search criteria are summarized in Table 1.

3.2. Empirical study

All the planned and exploratory analyses were performed with JASP software (2018) after collecting the data from all the participants ($N = 30$). Following our pre-registered plan of analyses (osf.io/wbeuy), for each participant and block of trials, valid RTs were computed by excluding the first two trials of each block (1.67%) as well as the incorrect responses (3.32%). Then the mean RTs were calculated, after eliminating trials with RTs smaller or larger than three standard deviations from the mean per participant and block (1.43%). Trials preceded by an error as well as those preceded by a control trial were also excluded, to avoid, respectively, a post error slowing and sequential effects, if not otherwise specified. In order to compute the percentage of correct responses,

Table 1 – Summary of the current existing literature (in chronological order), in which non-invasive brain stimulation techniques have been used to modulate the activity of DLPFC and observe stimulation aftereffects on either the acquisition of ISL. *SRT*=Serial Reaction Time task, *ASRT* = Alternating Serial Reaction Time task, *TSL* = Task Sequence Learning, *(HD-)tDCS* = (high density) transcranial direct current stimulation, *rTMS* = repetitive transcranial magnetic stimulation, *cTBS* = continuous theta burst stimulation, n.s.: non-significant results.

Authors	Task	Stimulation parameters	Stimulation site	Stimulation timing	Learning assessment	Stimulation effects on learning
Nitsche et al. (2003)	Unimanual and deterministic SRT	Two groups (i.e., stimulation site, N = 40) with within-group manipulations (same sequence) -Experimental condition: anodal and cathodal tDCS (1 mA intensity, 15 min) separated by 1 week -Control condition: sham stimulation, separated by 1 week	Contralateral to task hand -Lateral PFC: 5 cm forward to C3 -Medial PFC: above orbita	**During** learning acquisition	During task execution	n.s.
Wilkinson et al. (2010)	Probabilistic SRT task	-Experimental group (N = 8): Inhibitory cTBS -Control group (N = 8): sham stimulation	-Left DLPFC: 5 cm anterior to hand representation in M1	**Before** learning acquisition:	During task execution	n.s.
Janacsek et al. (2015)	ASRT	-Experimental groups (i.e., 2, N = 30): anodal 1 mA tDCS for 10min -Control group (N = 15): sham stimulation	-Left DLPFC: F3 -Right DLPFC: F4	**During** learning acquisition	During task execution, immediately after and after 2 and 24 h	Anodal stimulation over Right DLPFC increased ISL consolidation after 2 and 24 h compared to sham stimulation
Ambrus et al. (2020)	ASRT	-Experimental group (N = 16): sequential inhibitory 1 Hz rTMS on both hemispheres -Control group (N = 16): sham stimulation	-Left DLPFC (MNI x = −37, y = 33, z = 32) -Right DLPFC (MNI x = 37, y = 33, z = 32)	**During** learning acquisition:	During task execution and after 10 min, 2 h and 24 h	Sequential inhibition of Left and Right DLPFC increased ISL consolidation after 24 h compared to sham stimulation
Savic, Cazzol et al. (2017) Experiment 1	Bimanual TSL	-Experimental groups (i.e., 4, N = 66): anodal and cathodal tDCS at 1 mA intensity for 30 min -Control groups (i.e., 2, N = 32): sham stimulation	-Left DLPFC: F3 -Right DLPFC: F4	**Before** and **during** learning acquisition	During task execution and after 24 h	n.s.
Experiment 2		-Experimental groups (i.e., 4, N = 64): anodal and cathodal tDCS at 1 mA intensity for 30 min -Control group (N = 16): sham stimulation		**During** acquisition: expression and cons		

(*continued on next page*)

Table 1 – (continued)

Authors	Task	Stimulation parameters	Stimulation site	Stimulation timing	Learning assessment	Stimulation effects on learning
Savic, Müri et al. (2017) Experiment 1	Unimanual TSL	-Experimental groups (i.e., 4, $N = 52$): anodal and cathodal tDCS at 1 mA intensity for 30 min -Control groups (i.e., 2, $N = 31$): sham stimulation	-Left DLPFC: F3 -Right DLPFC: F4	**During** learning acquisition	During task execution and after 24 h	n.s.
Experiment 2		-Experimental groups (i.e., 2, $N = 32$): inhibitory 1 Hz rTMS (Left DLPFC) or inhibitory cTBS (Right DLPFC) -Control group ($N = 16$): sham stimulation		**Before** (cTBS) and **during** (rTMS) learning acquisition		
Savic et al. (2019)	Bimanual TSL	-Experimental groups (i.e., 4, $N = 58$): anodal and cathodal HD-tDCS at 2 mA intensity for 20 min -Control groups (i.e., 2, $N = 31$): sham stimulation	-Left DLPFC: F3 -Right DLPFC: F4	**During** learning acquisition	During task execution and after 24 h	n.s.

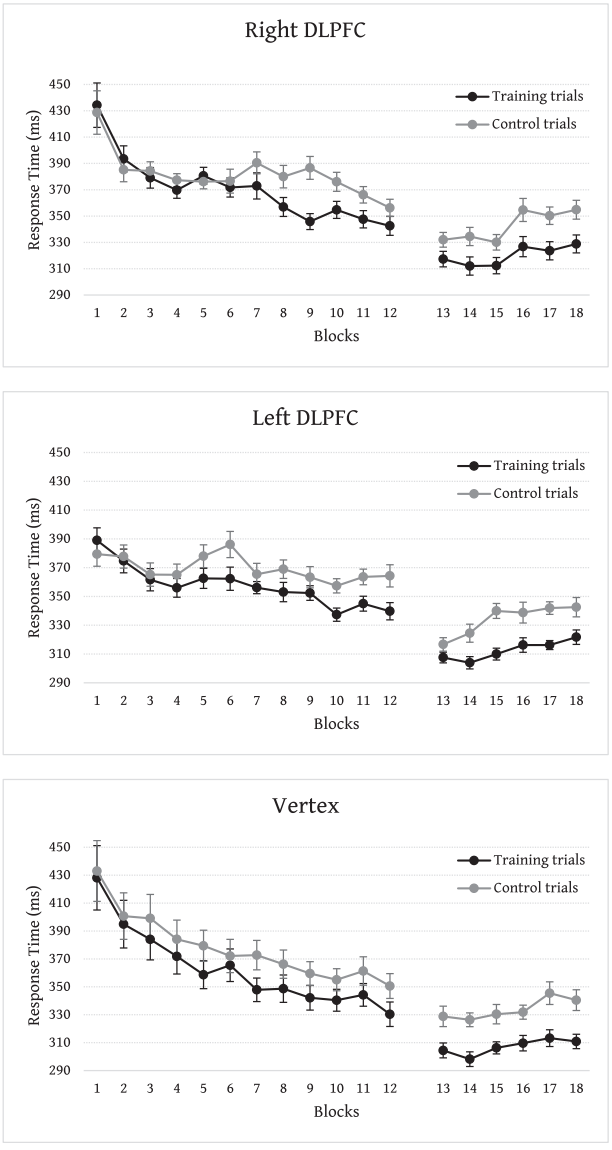

Fig. 4 – ISL (RTs) acquisition and expression in the three groups across the whole SRT task: participants became faster in response to the expected training trials, without difference between groups either before (blocks 1–12) or after the stimulation (blocks 13–18). Error bars represent standard errors.

the first two trials of each block were excluded, as well as trials preceded by a previous control trial, to avoid sequential effects, if not otherwise specified. The data from all the participants were considered for the analyses since nobody performed the task with an accuracy lower than 90% in any block ($M = 96.59\%$). RTs for correct responses and percentage of accuracy were computed separately for training and control trials. Following our preregistered inference criteria, the standard .05 alpha error probability was used as significance threshold for each frequentist analysis. In addition, for the non-preregistered Bayesian counterparts, we used a Bayes Factor, $BF_{10} \geq 6$ and $BF_{10} \leq 0{,}16$ as moderate evidence for or against the effect, as suggested for explorative purposes (Schönbrodt and Wagenmakers, 2018).

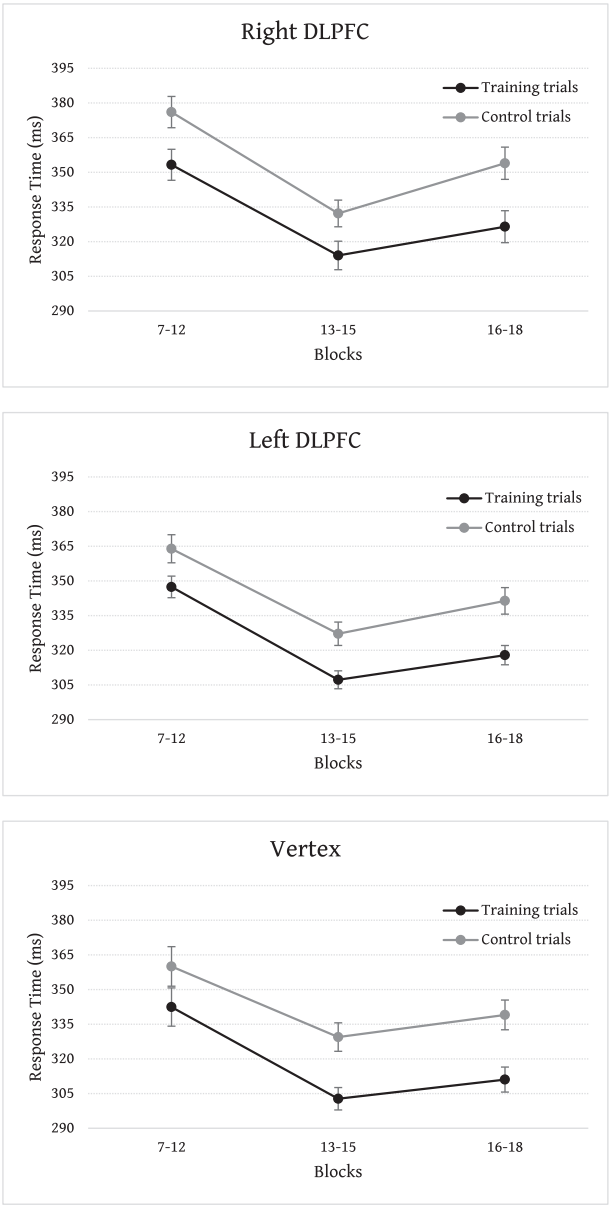

Fig. 5 – Comparison between the mean ISL index during the pre-stimulation baseline (blocks 7–12) and the mean ISL indices after the stimulation, during the first (13–15) or last post-stimulation blocks (16–18). ISL expression increased during blocks 16–18 compared to the baseline, but without significant differences between the three groups. Error bars represent standard errors.

3.2.1. *Implicit sequence learning*

A Group (3; Vertex, Right DLPFC, Left DLPFC) x Trial type (2; training *vs* control) x Blocks (1–12) ANOVA was carried out to investigate the acquisition of learning in the three groups across the initial training phase, before the stimulation. As highlighted in Fig. 4, the analysis showed a main effect of Trial type, F (1,27) = 53.366, $p < .001$, $\eta_p^2 = .66$, and a Trial type × Blocks interaction, F (11,297) = 3.266, $p < .001$, $\eta_p^2 = .11$, thereby participants being increasingly more rapid in response to training trials compared to control trials. Participants were also overall more rapid with practice, as shown by the main effect of Blocks, F (2.410, 65.073)[3] = 10.435, $p < .001$, $\eta_p^2 = .28$. The same analysis on error production confirmed that the three groups became overall more inaccurate across training, Blocks, F (11, 297) = 4.824, $p < .001$, $\eta_p^2 = .15$, but specifically more inaccurate to control trials compared to training trials, Trial type, F (1,27) = 33.124, $p < .001$, $\eta_p^2 = .55$, and suggested also an increase in learning expression across training in terms of accuracy as well, Trial type x Blocks, F (6.882,185.805)[1] = 2.373, $p = .02$, $\eta_p^2 = .08$. As expected for these pre-stimulation analyses, all these effects were independent of Group (*all ps* > .86).

As for the expression of learning after the stimulation, a Group (3; Vertex, Right DLPFC, Left DLPFC) x Trial type (2; training *vs* control) x Blocks (13–18) ANOVA confirmed an overall expression of ISL, Trial type, F (1,27) = 123.378, $p < .001$, $\eta_p^2 = .82$, as well as an overall increase in RTs across training, Blocks, F (5,135) = 9.074, $p < .001$, $\eta_p^2 = .25$. Importantly, however, none of these effects were modulated by the stimulation site, Group x Trial type, F (2,27) = .587, $p = .5$, Group x Blocks, F (10,135) = .916, $p = .52$. The analysis on error rates confirmed the overall learning expression in all the three groups, Trial type, F (1,27) = 38.757, $p < .001$, $\eta_p^2 = .59$, again independently of the stimulation group, Group x Trial type, F (2,27) = 1.818, $p = .182$.

Fig. 5 shows the critical analysis comparing learning expression before the stimulation (collapsed blocks 7–12) and soon after the stimulation (collapsed blocks 13–15) as well as during the last blocks after the stimulation (collapsed blocks 16–18), in order to highlight possible differences in time of stimulation aftereffects. The Group (3; Vertex, Right DLPFC, Left DLPFC) x Trial type (2; training *vs* control) x Blocks (7–12, 13–15, 16–18) ANOVA confirmed overall learning expression, Trial type, F (1,27) = 143.496, $p < .001$, $\eta_p^2 = .84$, and revealed a sudden decrease in RTs after the stimulation, Blocks, F (1.672,45.133)[4] = 89.716, $p < .001$, $\eta_p^2 = .77$. Interestingly, learning expression was different in the considered time points, as shown by the Trial type × Blocks interaction, F (2,54) = 3.636, $p = .03$, $\eta_p^2 = .12$. However, such a difference was not modulated by the stimulation site, as suggested by the non-significant Group x Trial type × Blocks interaction, F (4,54) = 1.064, $p = .38$. Separate comparisons confirmed that learning expression increased during blocks 16–18 compared to the learning index during blocks 7–12, Trial type x Blocks, F (1,27) = 7.065, $p = .01$, $\eta_p^2 = .21$, but that this increase was not differently modulated by the stimulation site, Group x Trial type x Blocks, F (2,27)<1, $p = .70$.

A Bayesian ANOVA with Group (3; Vertex, Right DLPFC, Left DLPFC) x Trial type (2; training *vs* control) x Blocks (7–12, 13–15, 16–18) ANOVA confirmed the main effect of Trial type, BF_{10} = 5.420e+32, as well as the main effect of Blocks, BF_{10} = 3.165e+20. However, learning expression did not appear to change across these blocks, as Bayesian evidence, $BF_{10} = .305$,

[3] Greenhouse-Geisser correction for violation of sphericity assumption.

[4] Huynh-Feldt correction for violation of sphericity assumption.

rather favoured the absence of Trial type × Blocks interaction. More importantly, Bayesian evidence supported that none of these effects was mediated by the type of stimulation, Group x Trial type, $BF_{10} = .134$, Group x Blocks $BF_{10} = .081$, Group x Trial type x Blocks, $BF_{10} = .163$. The analyses on error rates revealed that learning was not differently expressed in time or between groups in the abovementioned comparisons.[5]

3.2.2. *Congruency sequence effect*

Given that the emergence of the CSE is intrinsically dependent on the establishment of a stable learning index, the analysis on the prestimulation blocks considered blocks 7–12 as a valid learning baseline. However, as in Jiménez et al. (2009) and Prutean et al. (2020), we computed an index which attenuated episodic confounds, driven by possible negative priming effects and learning higher than second order contingencies. During those blocks, the Previous Trial type (training *vs* control) x Trial type (training *vs* control) ANOVA showed the presence of a significant CSE, Previous Trial type x Trial type, $F(1,27) = 10.849$, $p = .003$, $\eta_p^2 = .29$, independently of Group, $F(2,27) = .918$, $p = .41$. The same ANOVA performed on the poststimulation blocks showed that the CSE remained stable after stimulation, Previous Trial type x Trial type, $F(1,27) = 10.406$, $p = .003$, $\eta_p^2 = .28$, again independently of Group, $F(2,27) = .907$, $p = .42$. When the two periods were contrasted for explorative purposes, with a Group (3; Vertex, Right DLPFC, Left DLPFC) x Previous Trial type (training *vs* control) x Trial type (training *vs* control) x Block (2; 7–12 *vs* 13–18), the CSE resulted overall strong, Previous Trial type x Trial type, $F(1,27) = 18.454$, $p < .001$, $\eta_p^2 = .41$, without differences in time, $F(1,27) = .259$, $p = .61$, or between groups, $F(2,27) = .073$, $p = .93$. Fig. 6 shows the general CSE computed across blocks 7–18 in all the participants of the three groups.

A Group (3; Vertex, Right DLPFC, Left DLPFC) x Previous Trial type (2; training *vs* control) x Trial type (2; training *vs* control) x Block (2; 7–12 *vs* 13–18) Bayesian ANOVA confirmed the presence of ISL, Trial type, $BF_{10} = 1.312e{+}32$, the overall decrease in RTs after the stimulation, Block, $BF_{10} = 4.037e{+}12$, and an overall strong CSE, Previous Trial type x Trial type, $BF_{10} = 108.390$, without differences as a function of time, Previous Trial type x Trial type x Block, $BF_{10} = .256$ or between groups, Group x Previous Trial type x Trial type x Block, $BF_{10} = .445$, Group x Previous Trial type x Trial type, $BF_{10} = .320$.

3.2.3. *Cued generation task*

A Group (3; Vertex, Right DLPFC, Left DLPFC) x Generated Trial type (3; training, control, random) ANOVA highlighted a main effect of Generated Trial type, $F(2,54) = 27.706$, $p < .001$, $\eta_p^2 = .51$, not modulated by group, $F(4,54) = 1.265$, $p = .29$. Separate comparisons revealed that participants generated a larger number of successors according to either training ($M = 45.25\%$, $SD = 13.22$), $t(29) = 6.200$, $p < .001$, $d = 1.132$, CIs [.665, 1.587] or control ($M = 38.90\%$, $SD = 11.27$) sequences $t(29) = 5.479$, $p < .001$, $d = 1$, CIs [.554, 1.435] compared to any other random successors ($M = 15.84\%$, $SD = 15.03$) not corresponding to any of the two sequences. Furthermore, a separate comparison confirmed that the difference between the amount of training and control successors produced by the participants was not significant, $t(29) = 1.788$, $p = .08$.

4. Discussion

The aim of the present study was to account for the causal role of the DLPFC – a brain region engaged in cognitive control after conflict detection (Botvinick et al., 1999, 2001) – in the expression of ISL. The need for this work was motivated, on the one hand, by previous behavioural evidence showing that ISL expression is hindered by transient engagement in cognitive control (Jiménez et al., 2009; Prutean et al., 2020), as well as by shifts toward more control-demanding task sets (Vaquero et al., 2019) and, on the other hand, by a gap in the literature merging cognitive control, implicit learning and non-invasive brain stimulation, as this was the first study addressing the causal role of DLPFC top-down control on the automatic *expression* of ISL. The outcomes of our experiment will be described in the following sections, alongside with the discussion of the relevant studies – highlighted by our review of the literature – in which the activity of the DLPFC has been manipulated either before or during learning *acquisition*, in order to give a more general picture on the causal role of the DLPFC in both the acquisition and the expression of implicit learning.

4.1. *Control of implicit learning expression*

The outcomes of the present study replicated several previous findings (Jiménez et al., 2009; Prutean et al., 2020). Thus, participants acquired ISL despite the noisier training procedure (i.e., 80% training trials), as they responded faster to training than control trials and became more inaccurate to control than training trials. Moreover, despite the extensive training of this study (i.e., 2160 trials), sequence learning remained largely implicit, thereby confirming that target presentation according to a probabilistic trial-by-trial substitution procedure prevents the development of full sequence awareness. As in our previous experiments (Prutean et al., 2020), the implementation of task-irrelevant alerting cues in the SRT task speeded up the orienting of attention towards the targets

[5] Additionally, to control for a potential technical limitation, separate analyses considered the change in ISL expression before versus after the stimulation by contrasting the performance of the Vertex group with that of participants stimulated at their 77%–80% RMT (i.e., four participants of the Right DLPFC group, five participants of the Left DLPFC group) after testing for the equality of variances (Levene's test, all *ps* > .05). The Group (3; Vertex, Right DLPFC, Left DLPFC) x Trial type (2; training *vs* control) x Blocks (7–12, 13–15, 16–18) confirmed the overall decrease in RTs after the pause required by the stimulation procedure, Blocks, $F(1.471,23.535) = 37.871$, $p < .001$, $\eta_p^2 = .70$, Huynh-Feldt corrected, and that learning expression was overall significant in all the three groups, Trial type, $F(1,16) = 76.159$ $p < .001$, $\eta_p^2 = .83$. However, learning did not appear to be differently expressed across time, Trial type x Blocks, $F(2,32) = 2.279$, $p = .12$, in either group, Group x Trial type x Blocks, $F(4,32) = .765$, $p = .56$. The same comparison in terms of accuracy (in the mean accuracy of control trials during blocks 7–12 and 13–15 Levene's test was violated) confirmed that learning was not modulated across time or between groups, Group x Trial type x Blocks, $F(3.248,25.980) = 1.600$, $p = .21$, Huynh-Feldt corrected.

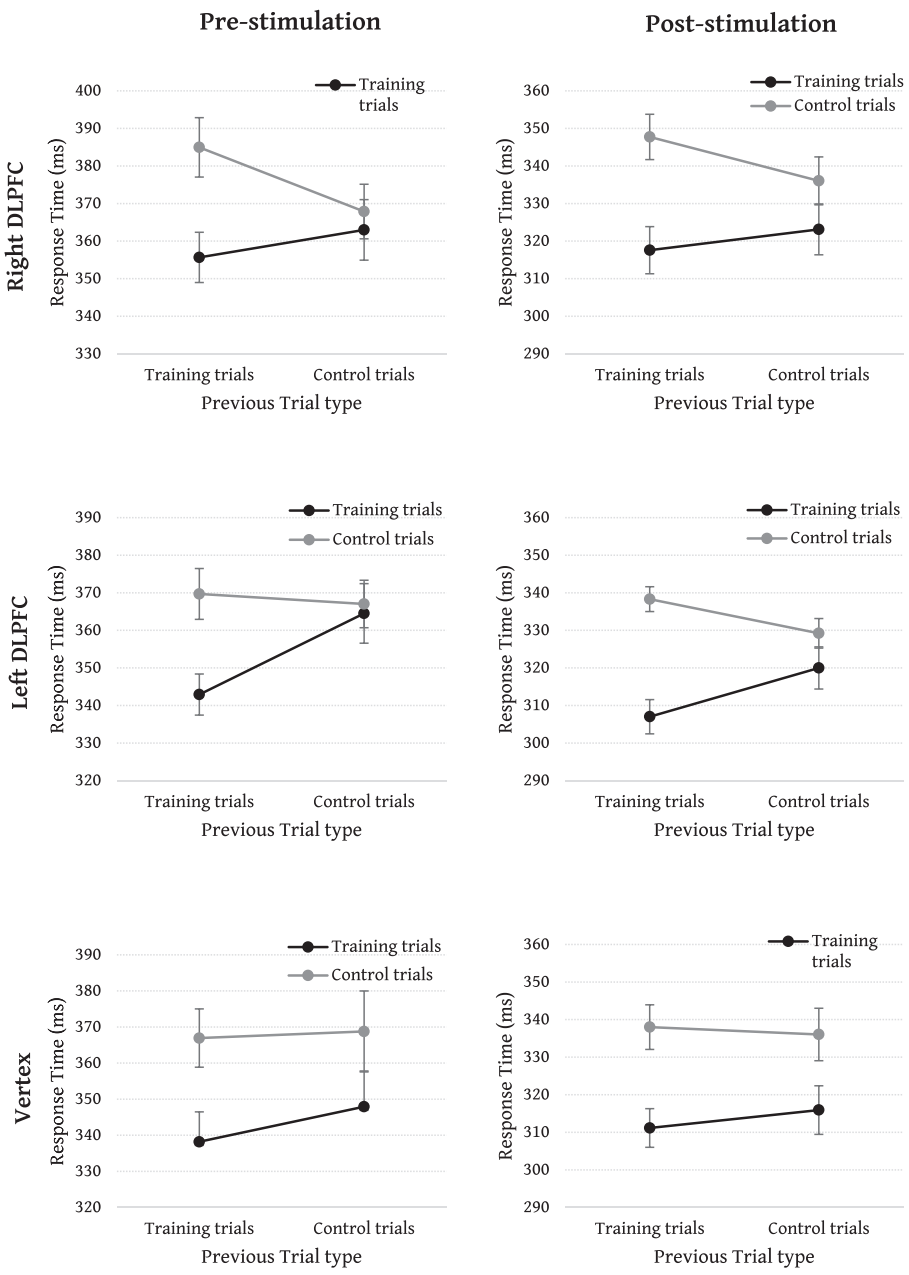

Fig. 6 – Averaged CSE during blocks 7–12 (pre-stimulation) and blocks 13–18 (post-stimulation), computed as in Jiménez et al., 2009 and Prutean et al., 2020. ISL is expressed mostly after training trials, while unexpected control trials trigger conflict and increase engagement in cognitive control, which in turn reduces the automatic expression of ISL. Error bars represent standard errors.

(Callejas, Lupiàñez, Funes, & Tudela, 2005; Posner, Snyder, & Davidson, 1980), reduced overall RTs (M_{RTs} = 356 msec), and boosted the emergence of the CSE, as compared to a previous study implementing the same manipulation without sounds (i.e., M_{RTs} = 406 msec, as reported in Prutean et al., 2020). Indeed, the CSE was overall strong, even when episodic confounds were controlled for (Jiménez et al., 2009; Prutean et al., 2020), thus challenging alternative associative accounts of this effect (Beesley et al., 2012).

However, the main aim of the present study was to provide evidence at the neural level of the behavioral effects linking increases in cognitive control with reductions in the expression of ISL (i.e., CSE, oddball-dependent sequence effect, and/or control-demanding task sets). In particular, we based our experimental hypotheses on the influential conflict monitoring model (Botvinick et al., 1999, 2001), which could not only account for our behavioral results, but also provide a hint on the neural basis of the conflict-control loop engaged in

those effects. In the present study, we addressed the relationship between cognitive control and ISL in the other way around as compared to previous behavioral evidence: rather than increase cognitive control-demands and observe reductions in ISL expression, we attempted to reduce cognitive control recruitments through inhibition of left and/or right DLPFC (as compared to an active stimulation of the Vertex) and hypothesized, as a consequence, an increase in ISL expression. However, the experimental outcomes presented here did not support such predictions: regardless of the stimulation site, all the three groups showed a significant decrease in RTs after the pause required by the cTBS application, as well as an increase in the expression of learning during blocks 16–18. Note that the potential technical limitations (i.e., a maximum of 48% MSO intensity allowed for the cTBS protocol) cannot explain the absence of an effect, since separate analyses taking into account only participants of the two experimental groups who were stimulated at their 77–80% RMT MSO also confirmed that the expression of learning after the stimulation was similar to that shown by the control group. More importantly, the Bayesian analyses highlighted moderate evidence against an effect of the stimulation in the experimental groups compared to the active control group (i.e., BF1≤0,16 for all contrasts of interest), which is recommended as conclusive evidence in the context of exploratory studies (Lee & Wagenmakers, 2013; Schönbrodt & Wagenmakers, 2018). One can argue that for the initial sample size constraints this could reflect misleading evidence, and therefore conclude that moderate evidence is not enough. To the best of our knowledge, simulation tools for Bayesian ANOVA designs – which might objectively back up this argument – have not been published so far. Moreover, we suggest that the gathered evidence, even if not considered conclusive, it is interpretable in the Bayesian framework, thus valid (Schönbrodt & Wagenmakers, 2018), and can be considered a preliminary starting point for other laboratories willing to continue with the accumulation of evidence (Palfi & Dienes, 2020).

Nevertheless, different explanations for the null effect must be taken into account. In this sense, the interesting finding of the present experiment can be rather explained as the emergence of a vigilance decrement across prestimulation blocks, as signalled by its fast recovery (i.e., sudden decrease in RTs) after the pause required by the neuronavigated stimulation procedure. A similar gain in RTs performance has been previously observed across different sessions separated by variable delays in other implicit learning studies (e.g., 30 min, 5 h, or 24 h in Albouy et al., 2006 or 1 day in Jiménez & Vázquez, 2005). These benefits have been explained as due to the consolidation of general motor skill learning during the delay period. For example, Albouy et al. (2006) implemented an oculomotor ISL paradigm, in which participants learned a sequence of saccades toward a dot moving according to a regular sequence of positions, while performing a covert task which guaranteed attentional selection of the sequence-relevant stimuli (i.e., to detect a color change in the moving dot). After training, participants acquired oculomotor ISL by showing increased oculomotor RTs when a new sequence was introduced in separate blocks of trials. Interestingly, when they were tested again, after a 30 min consolidation period, the authors highlighted a decrease in oculomotor RTs, although mostly for training trials (i.e., 32 msec *vs* 18 msec for control trials, which – however – were introduced in a separate block, and not immediately after the delay). Similarly, Meier and Cock (2014) observed a decrease in RTs for both training and random trials when comparing performance in an ASRT task in two different sessions, separated by either 24 h or 1 week of offline consolidation. In addition, Nemeth et al., 2010 reported a similar improvement in overall RTs during ASRT task performance, after a 12 h interval including either a period of sleep or wake between sessions, suggesting again an offline consolidation of general motor skills, but independent of sleep consolidation.

To the best of our knowledge, no study has previously observed a similar recovery of RTs in the ISL paradigm after just a 5 min delay, which seems reasonably too short for consolidation to take place: in the present study, participants of all the three groups were faster after the 5 min pause required by the stimulation procedure in response to either training (by 40 msec, on average) or control trials (by 37 msec, on average). Therefore, the reduced RTs observed in our study, and the larger learning effect observed in other studies, might be due to the recovery of vigilance rather than to consolidation of learning. Indeed, our results could indicate that the common measure of the acquisition and expression of ISL across a SRT task (i.e., a larger decrease in RTs to training trials compared to control trials across training blocks) might actually be an additive measure of both ISL acquisition (which makes responses to training faster than to control trials across time on task) and vigilance decrement (which makes overall responses slower across time on task). Moreover, given that ISL expression is mainly observed as a response facilitation (i.e., decrease in RTs) to training trials, we acknowledge that the mandatory pause and the consequent recovery from the vigilance decrement (as observed in our data) could have masked subtle effects of the stimulation in the two experimental groups, even though the same effect was observed in the Vertex stimulation group.

A less speculative explanation of this null effect would concern the stimulation sites used in the present experiment though. The stimulation coordinates were extracted from a previous study (Cieslik et al., 2012), which applied a functional connectivity analysis on the data coming from several experiments, in order to identify prefrontal involvements in executive motor control. In particular, in accordance with the conflict monitoring account (Botvincik et al., 1999, 2001), we referred to the MNI coordinates of a portion of DLPFC involved in a more anterior-ventral network and which resulted functionally more connected to the ACC. However, the involvement of the conflict-control loop could actually explain transient modulations of automatic behavioral performance, as in the CSE or the oddball-dependent sequence effect (Jiménez et al., 2009; Prutean et al., 2020). Similarly, the DLPFC could be recruited also during more tonic engagements in cognitive control (Braver, 2012) as suggested by previous behavioral evidence during more control-demanding versions of the SRT task (Vaquero et al., 2019). However, in the present study we did not overlty manipulate the engagement in either tonic (e.g., presence of distracters in Vaquero et al., 2019) or transient cognitive control (e.g., presence of incongruent trials

in Vaquero et al., 2019, or oddball sounds in Prutean et al., 2020). At the same time, the current study lacked the required sample size (i.e., 24 participants per group, based on Prutean et al., 2020) to observe possible stimulation aftereffects on more transient and subtle control engagements arising throughout the learning process, as indexed by the CSE (Jiménez et al., 2009; Prutean et al., 2020). Hence, we surmise that the inhibition of the DLPFC, as part of a network involved in executive motor control (Cieslik et al., 2012), did not modulate the tonic expression of ISL after extensive training with a probabilistic version of the SRT task, which – indeed – did not overtly demand for engagement in cognitive control.

4.2. *Control of implicit learning acquisition*

The second aim of the present work was to exhaustively review the existing literature on the modulation of DLPFC activity by means of non-invasive brain stimulation techniques, to highlight its role, as a region engaging cognitive control (Botvinick et al., 1999, 2001; Miller & Cohen, 2001), in controlling automatic implicit learning. The seven studies fulfilling our search criteria modulated DLPFC activity either before or during the acquisition of implicit learning and are summarized in Table 1. As can be observed, they include three studies implementing the STL paradigm (Savic, Cazzoli, Müri, & Meier, 2017; Savic, Müri, & Meier, 2017, 2019), two more studying the same questions in the context of ASRT paradigm (Ambrus et al., 2020; Janacsek, Ambrus, Paulus, Antal, & Nemeth, 2015), and two using either deterministic or probabilistic versions of the SRT task (Nitsche et al., 2003; Wilkinson, Teo, Obeso, Rothwell, & Jahanshahi, 2010).

From those studies investigating the role of DLPFC in the acquisition of TSL, none of them found a significant modulation of implicit learning after either inhibiting the DLFPC or modulating its cortical excitability. Interestingly, the TSL paradigm allows also the measurement of shift costs, which emerge when participants shift from one task to the other and are known to rely on PFC functioning (Braver, Reynolds, & Donaldson, 2003; Hyafil, Summerfield, & Koechlin, 2009). Given that the tDCS modulation (Savic, Müri et al., 2017) did not have an effect on switch costs either, the authors considered the stimulation in that study as suboptimal – mainly in terms of spatial specificity – to properly modulate the activity of the DLPFC and observe behavioral effects. However, the experiments implementing more focal stimulations (Savic, Cazzoli, et al., 2017; Savic, Müri, & Meier, 2019) also confirmed the null effects on both implicit learning modulation and switch costs. We suggest that null effects in all these studies were probably due to a lack of stereotaxic coregistration of the stimulation site, which was indeed localized on the basis of the standard 10–20 EEG system. Rather than (or besides to) the focality of the stimulation, perhaps the stimulation site was not adequate to stimulate that portion of the DLPFC involved in executive (motor) control.

In contrast to the studies involving the TSL task, the two studies implementing the ASRT task (Ambrus et al., 2020; Janacsek et al., 2015) both found a significant increase in implicit learning expression after a consolidation period when either the right or both the left and right DLPFC were inhibited during training. Ambrus et al. (2020) interpreted this increased automatic implicit learning as due to a competition between two different ways of picking up statistical regularities in the environment: one based on a hypothesis-driven system (Abrahamse et al., 2010), disrupted in the two studies, and another based on a striatum-mediated procedural system, favored by such disruption. However, as tempting as this interpretation sounds, the outcomes of these two studies cannot be considered conclusive, because none of them had a formal assessment of sequence awareness, which is a prerequisite to define sequence learning as implicit. As such, we cannot conclude that the inhibition of the DLPFC (or a decrease in its cortical excitability by tDCS) had an effect on the acquisition of implicit learning, as measured through the ASRT task.

Finally, as for the studies implementing the SRT task (Nitsche et al., 2003; Wilkinson et al., 2010), neither of them found a significant modulation of implicit learning either. In particular, the study by Wilkinson et al. (2010) was the one which better resembled the probabilistic SRT task implemented in our experiment, even though it lacked stereotaxic coregistration, but the outcomes of that study disconfirmed a causal role of the DLPFC in implicit learning acquisition as well.

To summarize, just two of the seven studies included in the review have found a significant increase in learning expression after inhibiting the DLPFC during learning acquisition with the ASRT task. However, this outcome should be taken cautiously, since both studies lacked a formal assessment of the implicitness of the learning process. As a whole, we suggest that the preliminary evidence against a role of DLPFC top-down control in the expression of ISL observed in our exploratory study is mirrored in the literature by a similar lack of effect on the acquisition of related forms of implicit learning after analogous modulations of DLPFC activity.

5. Conclusion

In the present work, we have pictured the state of the art of the literature merging cognitive control, implicit learning, and non-invasive brain stimulation techniques, in order to investigate the causal contribution of the DLPFC to implicit learning performance. Previous studies have experimentally manipulated the activity of the DLPFC (or its cortical excitability by means of tDCS) before and/or during the *acquisition* of implicit learning, while the present study was the first – to the best of our knowledge – to use a causal approach to tackle its role in the *expression* of implicit learning. Considering the outcomes of the present study in the context of the existing literature, we conclude that, up to date, there is not sufficient evidence supporting a causal role of DLPFC in the inhibition of either the acquisition or the expression of implicit learning.

In particular, previous behavioural evidence suggesting a modulation of the expression of implicit learning by cognitive control was found in paradigms implementing probabilistic versions of the SRT task (Jiménez et al., 2009; Prutean et al., 2020; Vaquero et al., 2019) but, consistent with the outcome of our experiment, Wilkinson et al. (2010) did not find an involvement of the DLPFC in the acquisition of such forms of ISL. The behavioural evidence of cognitive control found in the above-mentioned literature referred to subtle and transient modulations, such as the CSE which, if removed by the

inhibitory stimulation, might have provoked a relative increase in the observed expression of ISL. However, the results indicated that the CSE was observed analogously before and after stimulation, with no significant modulation of learning either. Thus, the present results add to the still recognizable low number of studies which have attempted to show a causal link between the inhibition of DLPFC and either the acquisition or the expression of ISL. It is particularly intriguing that only the two studies that implemented the ASRT paradigm reported a significant effect of this manipulation, and only on the consolidation of this learning. At present, the evidence in favor of such a causal role is therefore only weak, and future studies should clarify any potential role of the DLPFC in the acquisition and expression of ISL, as well as the neural correlates of those transient modulations of ISL which appear to be driven by rather more subtle oscillations of control.

Authors contribution

N.P. – Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original draft, Visualization; E.M.A. – Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original draft, Visualization, Supervision; A.L. – Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original draft, Supervision; L.J. – Conceptualization, Methodology, Formal analysis, Writing – Original draft, Supervision; A.V. – Conceptualization, Methodology, Writing – review and editing, Supervision; J.L. – Conceptualization, Methodology, Formal analysis, Writing – Original draft, Supervision, Project administration, Funding acquisition.

Open practices

The study in this article earned Open Data, Open Materials and Preregistered badges for transparent practices. Materials and Data for this study can be found at https://osf.io/rnq2f/.

The present experiment was pre-registered with Preregistration Template from AsPredicted.org. Portions of these findings were presented as a poster at the 2019 Rovereto Attention Workshop (RAW), Rovereto, Italy.

Declaration of competing interest

None.

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Supplementary data

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