Neuropsychologia 135 (2019) 107242

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: http://www.elsevier.com/locate/neuropsychologia

Time course of the inhibitory tagging effect in ongoing emotional processing. A HD-tDCS study

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ARTICLE INFO

Keywords:
Inhibitory tagging
Inhibition of return
HD-tDCS
Emotional conflict effect

ABSTRACT

When a cueing procedure that usually triggers inhibition of return (IOR) effects is combined with tasks that tap semantic processing, or involve response-based conflict, an inhibitory tagging (IT) emerges that disrupts responses to stimuli at inhibited locations. IT seems to involve the executive prefrontal cortex, mainly the left dorsolateral prefrontal cortex (DLPFC), in cognitive conflict tasks. Contrary to other inhibitory effects, IT has been observed with rather short intervals, concretely when the stimulus onset asynchrony (SOA) between the prime presented at the cued location, and the subsequent target is 250 ms. Here we asked whether IT is also applied to ongoing emotional processing, and whether the left DLPFC plays a causal role in IT using HD-tDCS. In two experiments with an emotional conflict task, we observed reduced conflict effects, the signature of IT, when the prime word was presented at the cued location, and once again when the prime-target SOA was just 250 ms. Also, the IT effect was eliminated when cathodal stimulation was applied to the left DLPFC. These findings suggest that the IT effect involves areas of the executive attention network and cooperates with IOR to favor attentional allocation to novel unexplored objects/locations, irrespective of their emotional content.

1. Introduction

We routinely perform different visual search behaviors that have been optimized through a long evolutionary process. To guarantee success in the resolution of these visual search tasks, our cognitive system activates some processes that bias our attention towards locations not previously inspected. The inhibition of return (IOR), originally described by Posner and Cohen (1984), is one of them.

The IOR has been mostly studied through a cue-target paradigm, showing a cost (greater reaction time, RT) when the target appears at the previously cued location compared to when it appears at the uncued location. In addition, for this effect to manifest two other conditions must be met: the time elapsed between the appearance of the cue and the target (stimulus onset asynchrony, SOA) should be greater than 300 ms, and the peripheral cue should not provide information about the location of the forthcoming target (see Klein, 2000 for a review).

Aside the long-lasting debate about the processes/mechanisms involved in IOR, with different researchers supporting different accounts of the effect (see Dukewich and Klein, 2015 for a survey among experts in the IOR field), Fuentes and collaborators claimed that ongoing processing of stimuli at locations subject to IOR is strikingly modulated. By using a cueing procedure that usually triggers IOR effects, combined with tasks that measure typical semantic priming or interference effects (e.g. the Stroop task), we could compare processing of stimuli in a control uncued condition with processing in an inhibited cued location. For instance, Fuentes et al. (1999; see also Vivas et al., 2007) combined the cuing procedure with semantic priming (Experiments 1 and 2) and flanker (Experiments 3 and 4) tasks in order to determine how the processing of stimuli was affected at the cued location. Whereas for stimuli presented at the uncued location the typical semantic priming and flanker interference effects were observed, for stimuli at the cued location semantically related stimuli and congruent flankers yielded longer RTs than semantically unrelated and incongruent ones. In order to illustrate how IT works, Fuentes and co-workers argued that the meaning of the prime word was preserved when presented at the cued location, but any response associated with the prime semantic category

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https://doi.org/10.1016/j.neuropsychologia.2019.107242
Received 26 February 2019; Received in revised form 16 October 2019; Accepted 29 October 2019
Available online 2 November 2019

would be affected by IT. If the forthcoming target, which is also located at the same location of the prime, is a semantically related target word, response will be affected, as such response has already been "tagged" with inhibition. Fuentes and collaborators extended the disruptive processing of stimuli at the cued location to other conflict paradigms such as the Stroop task (Vivas and Fuentes, 2001). In the Stroop study, the interference effect was not reversed but significantly reduced when stimuli were presented at the cued location compared to when they were presented at the uncued location. The authors proposed that IOR generates an inhibitory tagging (IT) that disrupts responses to stimuli at the inhibited location, producing the aforementioned distortion in the typical effects.

Caution is needed here to differentiate what we call "inhibitory tagging", affecting the access to the response system of stimuli presented at cued locations, from the reference to "inhibitory tags" to spatial locations that has been proposed by some authors to account for the IOR effect (Sapir et al., 2004; Van Koningsbruggen et al., 2009). Given the similarity in terminology and the fact that IT is assumed to emerge in cueing procedures that usually produce IOR effects, Fuentes and co-workers claimed that IOR and IT are two distinct, dissociable, inhibitory effects. Evidence for such dissociation comes from neuroimaging research (Chen et al., 2006; Zhang et al., 2012), neuropsychological studies with brain-damaged (Vivas et al., 2003) and psychiatric patients (Fuentes et al., 2000), and normal aging (Langley et al., 2005). Regarding IOR, neuroimaging and patient studies show a bulk of evidence that involves the superior colliculus (Berger and Henik, 2000; Sapir et al., 1999), and areas of the dorsal frontoparietal network in the generation of spatial-based IOR (Bartolomeo et al., 2001; Bourgeois et al., 2013; Chen et al., 2010; Dorris et al., 2002; Van Koningsbruggen et al., 2009; Mayer et al., 2004; Ro et al., 2003; Sapir et al., 2004; Vivas et al., 2003, 2006; Vivas et al., 2019). Regarding IT, frontal areas, mainly the left dorsolateral prefrontal cortex (DLPFC), have been implicated in the generation of IT (Chen et al., 2006; Zhang et al., 2012).

Dissociation between IOR and IT is also supported by the different time course of both effects at both the neural and the behavioural levels. For instance, in studies that used event-related potentials (ERP), early components such as P1 and N1 have been associated with IOR whereas late components such as N450 have been associated with IT (Zhang et al., 2012). Behaviourally, the IOR effect is apparent with rather long cue-target intervals when discrimination tasks are used (see Lupiáñez et al., 1997). The IT effect manifests just when the target follows the prime by a short SOA. With longer SOAs the IOR effect is still present (Langley et al., 2007) whereas the IT effect vanishes away after a prime-target SOA of 250 ms. (Fuentes et al., 1999; Vivas and Fuentes, 2001).

The present study is concerned with IT rather than IOR. To date the different studies concerned with IT have been conducted using cognitive tasks where semantic processing is involved (e.g. Chen et al., 2006; Fuentes et al., 1999; Vivas and Fuentes, 2001). Importantly, although cognitive and affective processes can be dissociated, there is much evidence that they interact (see Pessoa, 2008). Neuroimaging studies have revealed that both types of processing share a set of common areas including the prefrontal cortex, as well as a common conflict-monitoring system located in the anterior cingulate cortex (Egner et al., 2007; Etkin et al., 2011; Kerns et al., 2004). Therefore, as it happens with cognitive conflict tasks, it is reasonable to assume that IT affects also ongoing emotional processing. Recently, Zhao et al. (2017) conducted a study in which they combined a task of emotional conflict with an IOR procedure. In their study they used stimuli in which a male or female face appeared with an emotional expression (relevant dimension) positive or negative. Embedded in the face appeared a word (irrelevant dimension) congruent or incongruent either with the sex of the face (the cognitive task), or with the emotional expression of it (the emotional task). In the cognitive task the participants responded to the sex of the face, while in the emotional task they responded to the emotional expression of the face. The behavioural data showed similar effects between the task of emotional conflict and the task of cognitive conflict, that is, the congruency effect was reduced when the target was presented at the cued location compared to the uncued location, a result that the authors attributed to IT. In addition, the N450 component of the ERPs, traditionally associated with conflict processing, was absent for both types of tasks at the cued location, but not at the uncued location. These results suggest that IT has a similar influence on the control of cognitive and emotional processing.

In the present study, we modified the experimental procedure used by Zhao et al. (2017) with the objective of exploring the temporal course of IT with a task of emotional conflict. The experiments used the face-word Stroop task similar to that of Egner et al. (2007), which generates an emotional conflict (see Fig. 1). An emotional prime word was followed by a target face showing an emotional expression congruent or incongruent with the word. We manipulated the interval between onset of the prime word and onset of the target face (the prime-target SOA) in order to study the temporal course of IT in ongoing emotional processing. In previous studies with semantic priming (Fuentes et al., 1999) or Stroop-like tasks (Vivas and Fuentes, 2001) we explored a set of prime-target SOAs where 250 ms was the shortest one. The typical effect (semantic priming, Stroop interference) was altered at the 250 ms SOA and restored with longer SOAs. In Experiment 1, we used a set of prime-target SOAs where 250 ms was a midway value. If IT is blind to the type of stimuli being processed, as Zhao et al. (2017) suggest, we hypothesized that the emotional conflict effect will be reduced at the 250 ms SOA as in previous studies. However, due to the relevance of emotional stimuli for our survival, it might be possible that differences in the time course of the IT effect can emerge when emotion-based conflict is employed. Briefly, in the first experiment we aimed to determine whether 250 ms SOA is also the interval where IT operates in controlling emotional conflict. In addition, by including prime-target SOAs shorter than 250 ms, we aimed also to determine whether 250 ms is the end point of a short temporal window where IT works, or it is just the crucial temporal interval where the effect is observed.

Experiment 2 replicated the basic design of Experiment 1 but used high-definition transcranial direct current stimulation (HD-tDCS) when participants performed the task. The HD-tDCS is a form of non-invasive brain stimulation capable of modulating cortical excitability through the depolarization of the membrane in the neurons (anodal) or producing a cortical inhibition by hyperpolarization (cathodal) (Paulus, 2011). In Experiment 2, we inhibited the activity of the left DLPFC by cathodal high-definition transcranial direct current stimulation (HD-tDCS). That technique has been thought to allow establishing causal-effect relationships between brain structures and cognitive processes (Yavari et al., 2018). Here we aimed to find a causal relationship that involves the DLPFC in the effect of IT on emotional conflict as well. In a previous study with a color-word Stroop task, Chen et al. (2006) observed that the left DLPFC showed higher neuronal activity levels at the cued location, compared to the uncued location, establishing a relationship between that brain area and IT on cognitive conflict. In addition, previous studies that tested patients diagnosed with schizophrenia (Fuentes et al., 2000), or used ERPs (Zhang et al., 2012) pointed to areas of the frontal lobe as the ones involved in the IT effect. However, these previous studies do not allow us to establish a causal relationship attributed to the activation of the DLPFC in the IT effect.

According to the results of previous studies, we hypothesized that, around the 250 ms prime-target SOA, the suppression of the left DLPFC via cathodal HD-tDCS will make the IT effect (conflict reduction at the cued location) disappear. However, IT is expected to manifest in the control group that receives sham stimulation.

In summary, we aimed to further our understanding of IT occurring in an IOR procedure by addressing three important research questions. First, does IT occur also when people process emotion laden stimuli presented at locations subject to IOR? (Experiment 1). Second, does the prime-target interval of 250 ms depict the end point of a short temporal

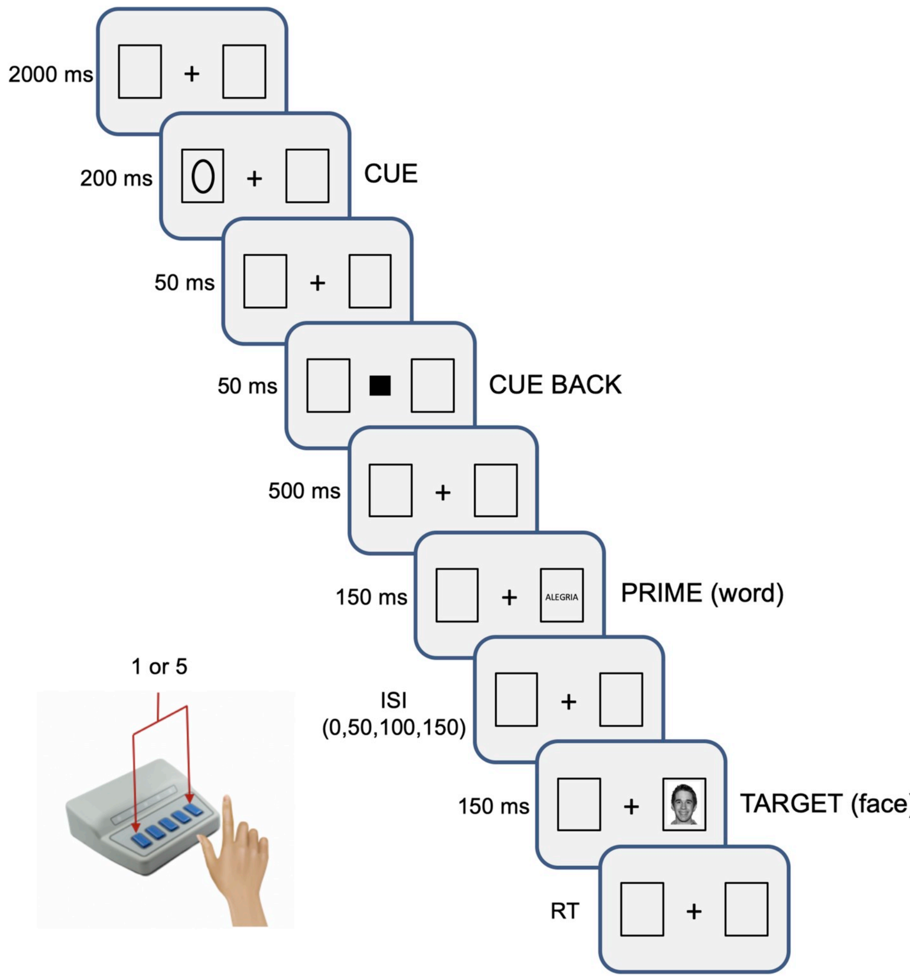

Fig. 1. Sequence of events and exposition duration of the stimuli. In Experiment 2 only the 50 and 100 ms intervals (200 and 250 ms SOAs, respectively) were used.

window where the IT effect works? (Experiment 1). Third, do the frontal areas, specifically the left DLPFC, play a key role in the generation of IT? (Experiment 2).

2. Methods

2.1. Participants

A group of 21 (17 females, mean age = 20.9 years; SD = 3.3) and a different group of 29 (19 females; mean age = 20.7; SD = 1.9) students of the University of Murcia took part in Experiments 1 and 2, respectively, in exchange for course credits. All participants reported normal or corrected-to-normal vision. Participants from Experiment 2 performed a previous screening with the HD-tDCS exclusion criteria (e.g. pregnancy, epilepsy, medication, use of pacemakers). The study was approved by the Ethics Committee of the University of Murcia and conformed with the Declaration of Helsinki for human research. Written informed consent was obtained from all participants.

2.2. Stimuli and procedure

We used two different images of a man's face selected from the NimStim Set of Facial Expressions (see Tottenham et al., 2009) with an expression of happiness (20_M_HA_O) or anger (20_M_AN_O) that served as the target stimulus. The objective of the task was to respond according to the happy or anger expression of the face. The Spanish words "ALEGRÍA" (HAPPINESS) or "ENFADO" (ANGER) served as the prime words. They were followed by the target face, which could depict with equal probability a congruent ("ANGER" - angry face, "HAPPINESS" - happy face) or incongruent ("HAPPINESS" - angry face, "ANGER" - happy face) emotional expression with the prime word. The pictures subtended a visual angle of approximately 4.4° x 5.7°, and the words a visual angle of 4.4° x 0.9°, with a distance to the screen of 65 cm. The experiment was programmed with the E-Prime 3.0 software (Schneider et al., 2002). The stimuli were presented on a 22″ TFT monitor, with 1920 × 1080 and 60 Hz resolution and the responses were collected through a Chronos® response box. The background color of the screen was white with stimuli in black.

The participants performed the experiment individually in sound-proof booths. Participants had to determine if the presented face expressed happiness or anger, by pressing keys 1 or 5 of the response box. The assignment of the keys to each of the two responses was counterbalanced across participants. The order of presentation of the trials in each block was determined randomly. In Experiment 1 there were three blocks of 128 trials each, with a short rest period between blocks. All participants completed 10 practice trials with feedback before the experimental trials, during which no feedback was presented. The procedure for each trial was as follows (Fig. 1). Each trial began with the presentation of a fixation cross in the center of the screen with two boxes on the sides for 2000 ms. Then, a cue (oval shape) appeared inside the left or right box (50% each), for 200 ms. After an interval of 50 ms, during which the fixation cross was displayed, the fixation cross was replaced by a black square (50 ms), and again the fixation cross appeared for 500 ms, followed by the prime word consisting of the words "HAPPINESS" or "ANGER". The prime word appeared with equal probability either in the same position as the cue (the cued location), or in the opposite position (the uncued location), during 150 ms. Subsequently, a cross fixation was presented in intervals of 0, 50, 100 or 150 ms, (corresponding to SOAs 150, 200, 250 and 300 ms, respectively) (Experiment 1). Next, the target face appeared always in the same position as the prime word and remained visible for 150 ms. Finally, a cross screen was presented until the response of the participants, and a new trial began. Note that the current procedure does not allow us to measure directly IOR effects because the emotional prime word did not require any response. However, the standard procedure used in the current experiments, in terms of the sequence and timing of events, has consistently yielded significant IOR effects in previous work in our lab (see Fuentes et al., 1999; Experiments 3 and 4), and in the IOR literature in general. Thus, we assumed that any effects observed at the cued location were due to this location being subject to IOR.

The stimuli and the procedure in Experiment 2 were identical to those of Experiment 1, except that only the 200 and 250 ms SOAs were used. That is, the SOA in which we observed a modulation of the emotional conflict effect by IT (250 ms) in Experiment 1, and other in which such modulation was not observed (200 ms). In total, the task was composed of 4 blocks with 128 trials per block. Previously, a block with 10 practice trials with feedback was presented. From the beginning of the practice block the tDCS stimulation was applied for a total duration of 20 min, a shorter duration than the one required for the participants to complete the task (32 min in average). Each participant was randomly assigned to one of the two conditions of brain stimulation: cathodal (14) or sham (15).

2.3. HD-tDCS protocol

We used a StarStim® wireless neurostimulator system (Neuroelectrics, Barcelona, Spain) in a novel 3×1 multifocal HD-tDCS montage with round Ag/AgCl electrodes (3.14 cm^2). The target area of stimulation was the left dorsolateral prefrontal cortex (DLPFC), which was located in F3 based on the 10–20 system. To optimize and focalize the stimulation, three other return electrodes were placed (T7, Cz and Fp2) with a 33% return of the current each, in a triangular scheme (Fig. 2). This multisite montage involves greater control over the focality and polarity of the effects (Kuo et al., 2013; Luft et al., 2017; Nikolin et al., 2015). In the cathodal stimulation condition, a constant current of 1 mA intensity was applied for 20 min with 30 s ramped up and 30 s ramped down at the start and at the end of the stimulation, respectively. The sham condition consisted in applying current only at ramp periods to emulate the skin tingling sensation. A double-blind design was used, that is, both the participants and the researcher in charge of administering the task were blind regarding the stimulation condition used for each participant. Both types of stimulation (cathodal and sham) were administered from the beginning of the task.

3. Results

3.1. Experiment 1

The mean of the correct RTs, the percentage of errors (PE), and congruency effects are shown in Table 1. Correct RTs were submitted to a repeated measured ANOVA with SOA (150, 200, 250, and 300 ms), location (cued and uncued) and congruency (incongruent and congruent) as the within-participants factors. We excluded trials with RTs shorter than 200 ms or longer than 1500 ms (0.46%). Error analyses did not yield any statistically significant result and they are not shown.

The results showed a main effect of congruency ($F_{1,\ 20} = 54.04$, $p < .001$, $\eta_p^2 = 0.730$). RTs were slower for the incongruent condition than for the congruent condition (588 vs. 554 ms). A main effect of SOA was also statistically significant ($F_{3,\ 60} = 13.08$, $p < .001$, $\eta_p^2 = 0.395$), with RTs of 587, 579, 564, y 554 ms, for SOA values of 150, 200, 250 y 300 ms, respectively. There was no main effect of location ($F_{1,\ 20} = 1.01$, $p = .327$, $\eta_p^2 = 0.048$). None of the first-order interactions reached statistical significance ($Fs < 1$). Most important, the three-way interaction SOA x location x congruency was significant ($F_{3,\ 60} = 2.89$, $p = .043$, $\eta_p^2 = 0.126$) (see Fig. 3). To further analyze this interaction, a separate ANOVA was conducted for each SOA value, with location and congruency as within-participants factors.

150-ms *SOA*. The main effect of congruency was significant ($F_{1,\ 20} = 16.21$, $p < .001$, $\eta_p^2 = 0.448$). RTs were slower for the incongruent condition than for the congruent condition (601 vs. 573 ms). No other effects were significant ($Fs < 1$).

200-ms *SOA*. The main effect of congruency was significant ($F_{1,\ 20} = 11.73$, $p < .001$, $\eta_p^2 = 0.370$). RTs were slower for the incongruent

Table 1
Mean of median reaction times (M) and percentage of errors (PE) as a function of location, congruency and prime-target SOA in Experiment 1.

Location	Incongruent		Congruent		Congruency Effect
	M	PE	M	PE	
SOA = 150 ms					
Uncued	599	10.0	572	7.0	27
Cued	604	10.0	574	7.0	30
SOA = 200 ms					
Uncued	594	11.0	569	4.0	25
Cued	590	11.0	565	8.0	25
SOA = 250 ms					
Uncued	582	12.0	527	4.0	55
Cued	583	10.0	566	6.0	17
SOA = 300 ms					
Uncued	576	12.0	532	5.0	44
Cued	579	10.0	530	6.0	49

Note — Congruency Effect = Incongruent - Congruent.

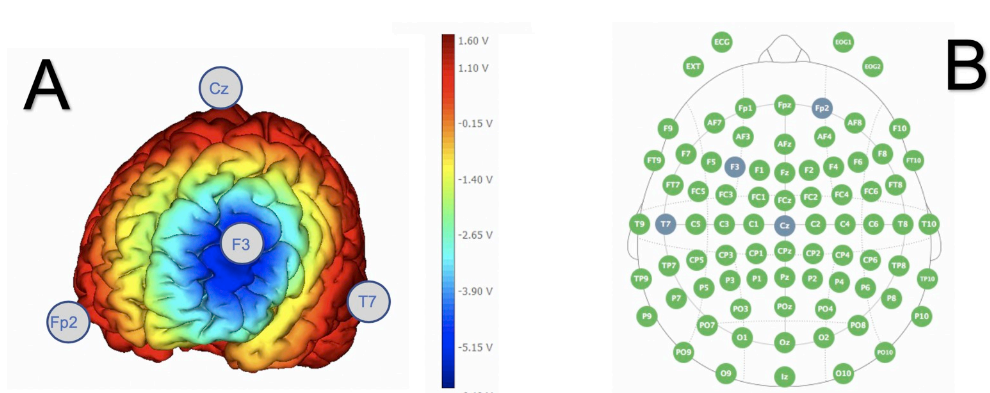

Fig. 2. (A) Simulation of the electric field according to the StimWeaver software (Neuroelectrics) based on a model derived from MR images and the Finite Element Method (Miranda et al., 2013) proposed in our protocol of stimulation. (B) Montage of the electrodes: F3 (target) and T7, Cz and Fp2 (return).

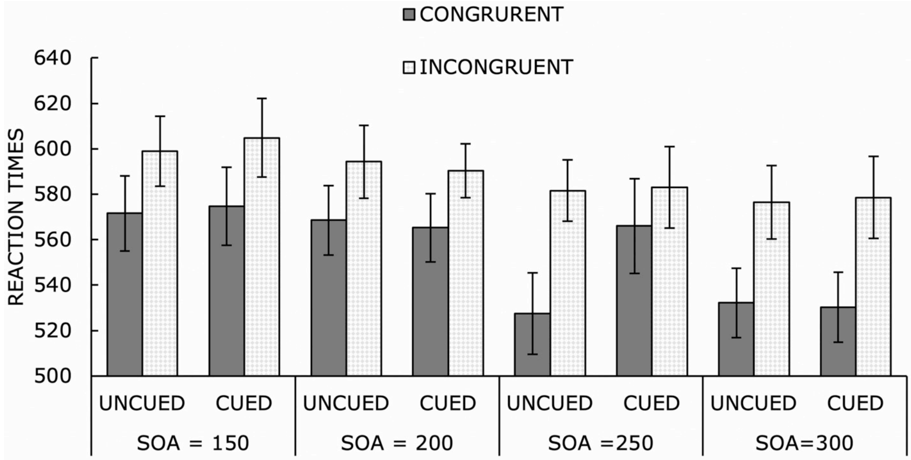

Fig. 3. The y axis represents the reaction times in the emotional conflict task of Experiment 1. SOA values were 150, 200, 250 and 300 ms. There is a reduction in the congruence effect for the SOA = 250 ms. The error bars represent the standard error of the mean.

condition than for the congruent condition (592 vs. 567 ms). No other effects were significant (*F*s < 1).

250-ms *SOA*. The main effect of congruency was significant ($F_{1, 120} = 15.127$, $p < .001$, $\eta_p^2 = 0.431$). RTs were slower for the incongruent condition than for the congruent condition (582 vs. 547 ms). The effect of location was marginally significant ($F_{1, 20} = 4.177$, $p = .054$, $\eta_p^2 = 0.173$). Most important, there was a significant location × congruency interaction ($F_{1, 20} = 16.58$, $p < .001$, $\eta_p^2 = 0.53$). Analysis of the simple main effects showed a significant congruency effect when the distractor was presented at the uncued location (55 ms) ($F_{1, 20} = 34.36$, $p < .001$, $\eta_p^2 = 0.539$), but not when it was presented at the cued location (17 ms) ($F < 1$).

300-ms *SOA*. The main effect of congruency was significant ($F_{1, 20} = 49.25$, $p < .001$, $\eta_p^2 = 0.711$). RTs were slower for the incongruent condition than for the congruent condition (577 vs. 531 ms). No other effects were significant (*F*s < 1).

3.2. Experiment 2

The mean of the correct RTs, the percentage of errors (PE) and congruency effects are shown in Table 2. Correct RTs were submitted to a mixed ANOVA with stimulation (cathodal and sham) as the between-participants factor and SOA (200 and 250 ms), location (cued and uncued) and congruency (incongruent and congruent) as the within-participants factors. We excluded trials with RTs shorter than 200 ms or longer than 1500 ms (0.38%). Error analyses did not yield any statistically significant result and are not shown.

Table 2
Mean of median reaction times (M) and percentage of errors (PE) as a function of stimulation, location, congruency and prime-target SOA in Experiment 2.

Stimulation	Location	Incongruent		Congruent		Congruency Effect
		M	PE	M	PE	
Sham	*SOA*= 200 ms					
	Uncued	566	12.0	522	6.0	44
	Cued	567	16.0	518	7.0	49
	SOA =250 ms					
	Uncued	563	12.0	489	6.0	74
	Cued	550	15.0	521	7.0	29
Cathodal	*SOA* = 200 ms					
	Uncued	538	12.0	503	6.0	35
	Cued	542	16.0	516	9.0	26
	SOA =250 ms					
	Uncued	527	17.0	492	7.0	34
	Cued	531	14.0	495	9.0	36

Note — Congruency Effect = Incongruent - Congruent.

The four-way stimulation x SOA x location × congruency interaction was significant ($F_{1, 27} = 7.848$, $p = .009$, $\eta_p^2 = 0.205$) (see Fig. 4), so we do not report any other effect for simplicity purposes. To further analyze this interaction, a separate repeated measures ANOVA was conducted for each stimulation group, with SOA, location and congruence as within-participants factors.

3.2.1. Sham stimulation

As in Experiment 1, the three-way SOA x location × congruency interaction was significant ($F_{1, 13} = 8.82$, $p = .011$, $\eta_p^2 = 0.404$). Accordingly, two separate ANOVAs for each SOA value (200 and 250 ms) were conducted, with location and congruence as within-participants factors.

200-ms *SOA*. The main effect of congruency was significant ($F_{1, 13} = 23.615$, $p < .001$, $\eta_p^2 = 0.645$). RTs were slower for the incongruent condition than for the congruent condition (520 vs. 566 ms). No other effects were significant (*F*s < 1).

250-ms *SOA*. The main effect of congruency was significant ($F_{1, 13} = 53.863$, $p < .001$, $\eta_p^2 = 0.806$). RTs were slower for the incongruent condition than for the congruent condition (557 vs. 505 ms). The effect of location was not statistically significant ($F_{1, 13} = 2.232$, $p = .159$, $\eta_p^2 = 0.147$). Most important, there was a significant location × congruency interaction ($F_{1, 13} = 10.32$, $p = .007$, $\eta_p^2 = 0.443$). The analysis of the simple main effects showed a significant congruency effect when the prime word was presented at the uncued location (74 ms), ($F_{1, 13} = 40.02$, $p < .001$, $\eta_p^2 = 0.755$). However, the congruency effect was reduced when the prime word was presented at the cued location (29 ms) ($F_{1, 13} = 14.29$, $p = .002$, $\eta_p^2 = 0.524$).

3.2.2. Cathodal stimulation

The results showed a main effect of congruency ($F_{1, 14} = 42.69$, $p < .001$, $\eta_p^2 = 0.753$). RTs were slower for the incongruent condition than for the congruent condition (534 vs. 502 ms). The main effect of SOA was also statistically significant ($F_{1, 14} = 20.07$, $p < .001$, $\eta_p^2 = 0.589$). There was no main effect of location ($F_{1, 14} = 1.94$, $p = .185$, $\eta_p^2 = 0.122$). None of the first-order interactions reached statistical significance, and most important, the three-way congruency x location × SOA interaction was not significant either (*F*s < 1).

4. Discussion

The aim of the present study was threefold. We aimed to; i) extend the IT effect that is usually observed at the cued (inhibited) location to ongoing emotional processing, ii) determine the emergence and development of IT in emotional conflict tasks, and iii) reveal whether the left

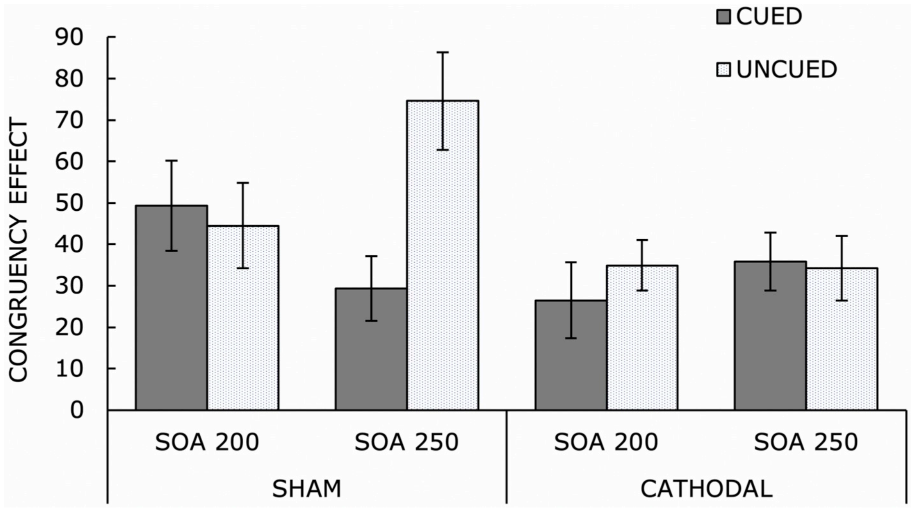

Fig. 4. The y axis represents the congruence effect (incongruent RTs - congruent RTs) in the emotional conflict task of Experiment 2. SOA values were 200 and 250 ms. There is a reduction in the congruence effect for the sham group (left part) with SOA = 250 ms. This reduction disappears by inhibiting the left DLPFC with cathodal tDCS (right part). The error bars represent the standard error of the mean.

DLPFC plays a key role in the generation of IT.

As with cognitive tasks, IT modulated ongoing emotional processing. We found the typical emotional conflict effect when the emotional prime word was physically separated from the target face, but the effect was eliminated (Experiment 1) or significantly reduced (Experiment 2, sham group) when the prime word was presented at the inhibited location. Importantly, such reduction in the emotional conflict effect, the signature of IT, was observed just with the 250 ms prime-target SOA, neither earlier nor later than that temporal interval. These results replicate previous ones with semantic priming (Fuentes et al., 1999) and Stroop-like interference effects (Vivas and Fuentes, 2001). Admittedly, we do not have yet an evidence-based account for the quick onset and decay of the IT. We can speculate, on the basis of other inhibitory effects, that inhibition takes some time to build up and it might explain why we did not observe IT effects with the shortest 150 ms SOA. The fact that it vanished away so quickly may reflect the adaptive value of this effect. In addition, the 250 ms SOA value likely reflects the timing necessary for the neural connections to take place. That is, the time required for the left DLPFC to send the inhibitory signal to the response system. Further neurophysiological studies that use precise timing of neural responses may clarify this issue.

In Experiment 2, we replicated the pattern of findings of Experiment 1 for the control group (sham stimulation). The IT modulation of the emotional conflict effect was observed again just with the 250 ms SOA. Furthermore, the suppression of the left DLPFC by the application of cathodal HD-tDCS yielded, as hypothesized, a lack of modulation of the emotional conflict effect when the prime word was presented at the cued location.

In determining how emotional congruency is affected by the IT, several accounts should be taken into consideration. One possibility is that as soon as the affective prime word is presented at the cued location, IOR delays processing of emotional information, reducing or eliminating the differences in reacting to the emotional expression of the target face, be that expression congruent or incongruent with the affect the prime word conveys. Against that explanation is the fact that with SOAs shorter or longer than 250 ms the emotional congruency effect was observed. That is, the affective prime word promptly contacted with its representation in the emotion processing system irrespective of whether it appeared at the cued or the uncued location, not being emotional processing affected by IT. Note that a similar account was raised by Fuentes and his co-workers when cognitive tasks were used (Fuentes et al., 1999; Vivas and Fuentes, 2001; Vivas et al., 2007; see Fuentes, 2004, and Fuentes et al., 2012, for reviews). For instance, with the cognitive semantic priming task, Fuentes et al. (1999) observed that when the prime word was presented at the cued location, related targets produced longer RTs than did unrelated ones. The fact that a semantic priming effect, although reversed, was observed at the cued location means that the prime word at that location contacted with its representation in the memory system. The standard semantic priming effect was restored with SOAs longer than 250 ms. The use of very short cue-target SOAs here represents stronger evidence against an explanation based on the assumption that accessing to the processing system by the affective prime word presented at the cued location is altered by IT.

As with other cognitive tasks, a more plausible explanation locates the IT effect at the response level. As previously mentioned, IT is also observed when the cueing procedure is combined with tasks that tap response-based conflict between competing stimuli/dimensions. For instance, when the task-irrelevant dimension (the word) was followed by the task-relevant dimension (a color patch) in a Stroop-like task, the interference effect was reduced/eliminated when the word was located at the cued location. Interestingly, the reduction in the interference effect was observed just in the 250 ms SOA, being restored with longer SOAs. With the flanker task, the flanker interference effect was reversed at the cued location, that is, congruent flankers produced longer RTs than incongruent flankers. Imaging studies also point to the response level as the stage where the IT operates. For instance, Chen et al. (2006) compared two incongruent conditions, one in which the color words denoted colors that did not belong to the response set (the incongruent-ineligible condition), and other in which the colors words denoted colors that belonged to the response set (the incongruent-eligible condition). Whereas in the former condition conflict occurred just at the pre-response level, in the later condition conflict occurred at both pre- and response levels. The left rostral anterior cingulate cortex was found to be involved in the IOR-conflict interaction at the pre-response level but increased left DLPFC activation was observed at the cued location in the response-eligible condition compared with the response-ineligible condition, a result that the authors interpreted as evidence of IT acting at the response level.

In the present study, we assume that emotional processing of the affective prime word is not affected at the cued (inhibited) location, but the access to the response is temporarily “disconnected” after 250 ms had elapsed. To illustrate the tagging process here, imagine that the prime word “angry” is presented at the cued location. Both the meaning and the emotional content of that word would be processed, but any response associated with such emotion would be temporarily affected by IT. If the forthcoming target depicts an angry face (the congruent condition) the participant's response will be hindered because the response "angry" has already been tagged with inhibition. Consequently, responses in the congruent condition will be delayed compared with when the prime word is presented at the control uncued location (Fig. 3 shows longer RTs in the congruent condition in the cued compared to the uncued location, in the 250 ms SOA). If instead the forthcoming target depicts a happy face (the incongruent condition), it mismatches with the emotion conveyed by the prime word (angry), in a similar way to the target unrelated word in the typical semantic priming task, but responses to the incongruent target face would not be affected by IT. Therefore, IT effects will be observed only in the congruent condition, slowing down responses to emotionally congruent targets, and accordingly reducing the emotional congruency effect just at the cued location. Fig. 5 illustrates how IT acts when the emotional conflict task is used in combination with the cueing procedure that triggers IOR.

Regarding the brain areas involved in the IT, previous studies with psychiatric patients pointed to the frontal lobe. For instance, Fuentes et al. (2000) used the combined cueing procedure and the Stroop task with outpatients diagnosed with schizophrenia. Whereas the patients showed preserved IOR and Stroop interference effects, they did not show any reduction in the Stroop effect when the targets were presented at the cued location. This finding is compatible with a deficit in the IT associated with the frontal disfunction that has been usually related to schizophrenia (see Weinberger, 1988), in line with other cognitive inhibition deficits involving the left hemisphere (see Fuentes et al., 1999). A more direct evidence of the involvement of the left DLPFC in IT comes from the fMRI study by Chen et al. (2006) and the EEG study by Zhang et al. (2012). In the present study we aimed to overcome the lack of causality that characterizes most of neuroimaging studies and establish a causal role of the left DLPFC in the IT. Here we took advantage of the multisite montage our high-definition tDCS permits to get greater control over the focality and polarity of the effects. With sham we replicated the results of Experiment 1 with just two crucial prime-target SOA values, one with the critical SOA of 250 ms where the IT effect was expected, and other with a shorter SOA of 200 ms where the IT effect was not expected. We preferred to use a SOA shorter rather than longer than 250 ms because in the previous cognitive tasks we always used 250 ms SOA as the shortest one. Note that the fact that standard emotional conflict effects are observed as early as 200 ms SOA reinforces our account that IT is affecting stages of processing occurring later than the ones involved in processing the emotional meaning of the prime word. On the basis of previous findings, we expected the suppression of the left DLPFC activity by cathodal stimulation to eliminate IT. Accordingly, we did not observe the typical reduction in the emotional conflict effect when the prime word was located at the cued location and the prime-target SOA was 250 ms. These results suggest a causal role of the left DLPFC in IT irrespective of whether processing involves emotional (present experiment) or cognitive conflict (Chen et al., 2006). The involvement of the prefrontal cortex in IT further supports the dissociation between IOR and IT, since this particular brain area has not been previously lined with the generation of IOR.

In our model, IOR and IT are two dissociable inhibitory mechanisms involving the orienting and the executive attentional networks, respectively. The presence of an uninformative spatial cue activates the frontoparietal network. The parietal lobe is thought to contain a spatial map where different locations differ in their relative salience so that the one containing the uninformative cue is tagged as inhibited (Vivas et al., 2003, 2006, 2019; see Fuentes, 2004, and Fuentes et al., 2012, for reviews). The frontoparietal network would translate the attention/oculomotor bias in subcortical structures (e.g., the superior colliculus) into a signal to areas of the frontal executive network implicated in response selection. The left DLPFC would be a crucial area of the network that interrupts any response already activated by the stimulus presented in the inhibited location. The 250 ms interval might reflect the time needed to accomplish such transient interruption.

The present and previous findings suggest that inhibitory mechanisms that rely on different attention networks interact in a cooperative way to favor attentional allocation to novel unexplored objects/locations, which suggests that search for novelty may be a pervasive characteristic of the attention system.

CRediT authorship contribution statement

Víctor Martínez-Pérez: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Alejandro Castillo:** Methodology, Investigation, Visualization. **Noelia Sánchez-Pérez:** Investigation, Writing - review & editing. **Ana B. Vivas:** Conceptualization, Writing - review & editing. **Guillermo Campoy:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Luis J.**

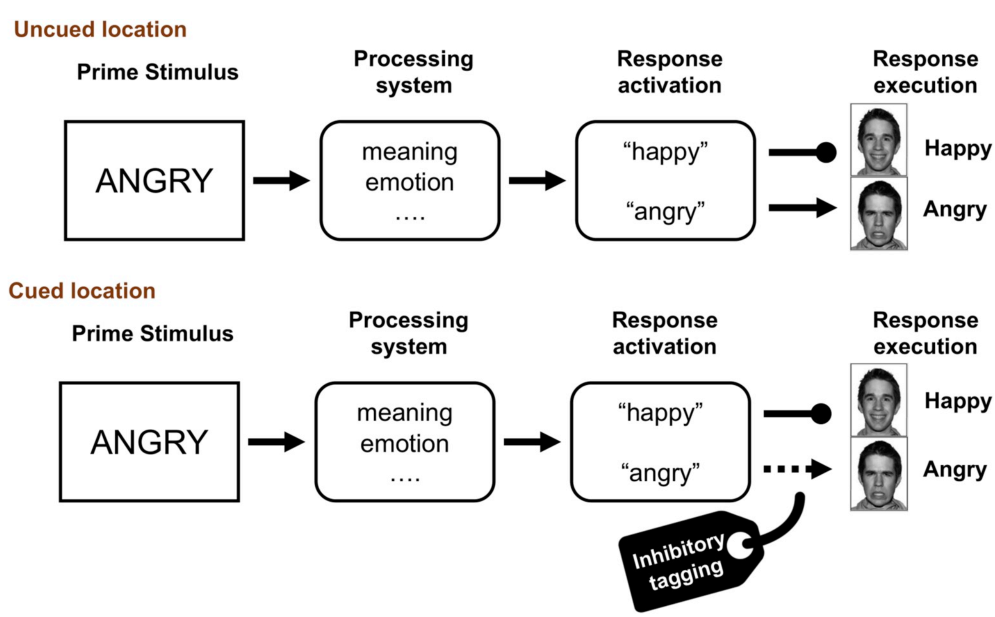

Fig. 5. Sequence of processing stages in the emotional conflict task as a function of the location of the affective prime word. The graph illustrates the stage of processing where IT is operating.

Fuentes: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Funding acquisition.

Acknowledgements

This work was supported by the Spanish Ministry of Economy, Industry and Competitiveness [project PSI2017-84556-P, FEDER funds], and the Spanish Ministry of Science, Innovation and Universities with a predoctoral grant (FPU17/00427).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2019.107242.

References

Bartolomeo, P., Siéroff, E., Decaix, C., Chokron, S., 2001. Modulating the attentional bias in unilateral neglect: the effects of the strategic set. Exp. Brain Res. 137 (3–4), 432–444.
Berger, A., Henik, A., 2000. The endogenous modulation of IOR is nasal-temporal asymmetric. J. Cogn. Neurosci. 12 (3), 421–428.
Bourgeois, A., Chica, A.B., Valero-Cabre, A., Bartolomeo, P., 2013. Cortical control of Inhibition of Return: exploring the causal contributions of the left parietal cortex. Cortex 49 (10), 2927–2934.
Chen, Q., Fuentes, L.J., Zhou, X., 2010. Biasing the organism for novelty: a pervasive property of the attention system. Hum. Brain Mapp. 31, 1146–1156.
Chen, Q., Wei, P., Zhou, X., 2006. Distinct neural correlates for resolving stroop conflict at inhibited and noninhibited locations in inhibition of return. J. Cogn. Neurosci. 18 (11), 1937–1946.
Dorris, M.C., Klein, R.M., Everling, S., Munoz, D.P., 2002. Contribution of the primate superior colliculus to inhibition of return. J. Cogn. Neurosci. 14 (8), 1256–1263.
Dukewich, K.R., Klein, R.M., 2015. Inhibition of return: a phenomenon in search of a definition and a theoretical framework. Atten. Percept. Psychophys. 77 (5), 1647–1658.
Egner, T., Etkin, A., Gale, S., Hirsch, J., 2007. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. Cerebr. Cortex 18 (6), 1475–1484.
Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn. Sci. 15 (2), 85–93.
Fuentes, L.J., Vivas, A.B., Langley, L.K., Chen, Q., González-Salinas, C., 2012. Inhibitory mechanisms in the attentional networks: A multidisciplinary approach. In: Posner, M.I. (Ed.), Cognitive Neuroscience of Attention, 2ª ed. Guilford Press, New York, pp. 76–88.
Fuentes, L.J., 2004. Inhibitory processing in the attentional networks. In: Posner, M.I. (Ed.), Cognitive Neuroscience of Attention. Guilford Press, New York, pp. 45–55.
Fuentes, L.J., Boucart, M., Vivas, A.B., Álvarez, R., Zimmerman, M.A., 2000. Inhibitory tagging in inhibition of return is affected in schizophrenia: evidence from the Stroop task. Neuropsychology 14, 134–140.
Fuentes, L.J., Vivas, A.B., Humphreys, G.W., 1999. Inhibitory tagging of stimulus properties in inhibition of return: effects on semantic priming and flanker interference. Q. J. Exp. Psychol. A Hum. Exp. Psychol. 52, 149–164.
Kerns, J.G., Cohen, J.D., MacDonald, A.W., Cho, R.Y., Stenger, V.A., Carter, C.S., 2004. Anterior cingulate conflict monitoring and adjustments in control. Science 303 (5660), 1023–1026.
Klein, R.M., 2000. Inhibition of return. Trends Cogn. Sci. 4 (4), 138–147.
Kuo, H.I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M.F., Nitsche, M.A., 2013. Comparing cortical plasticity induced by conventional and high-definition 4× 1 ring tDCS: a neurophysiological study. Brain Stimulation 6 (4), 644–648.
Langley, L.K., Fuentes, L.J., Vivas, A.B., Saville, A.L., 2007. Aging and temporal patterns of inhibition of return. J. Gerontol.: PSYCHOL. SCI. 62B, 71–77.
Langley, L.K., Vivas, A.B., Fuentes, L.J., Bagne, A.G., 2005. Differential age effects on attention-based inhibition: inhibitory tagging and inhibition of return. Psychol. Aging 20 (2), 356.
Luft, C.D.B., Zioga, I., Banissy, M.J., Bhattacharya, J., 2017. Relaxing learned constraints through cathodal tDCS on the left dorsolateral prefrontal cortex. Sci. Rep. 7 (1), 2916.
Lupiáñez, J., Milán, E.G., Tornay, F.J., Madrid, E., Tudela, P., 1997. Does IOR occur in discrimination tasks? Yes, it does, but later. Percept. Psychophys. 59 (8), 1241–1254.
Mayer, A.R., Seidenberg, M., Dorflinger, J.M., Rao, S.M., 2004. An event-related fMRI study of exogenous orienting: supporting evidence for the cortical basis of inhibition of return? J. Cogn. Neurosci. 16 (7), 1262–1271.
Miranda, P.C., Mekonnen, A., Salvador, R., Ruffini, G., 2013. The electric field in the cortex during transcranial current stimulation. Neuroimage 70, 48–58.
Nikolin, S., Loo, C.K., Bai, S., Dokos, S., Martin, D.M., 2015. Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning. Neuroimage 117, 11–19.
Paulus, W., 2011. Transcranial electrical stimulation (tES–tDCS; tRNS, tACS) methods. Neuropsychol. Rehabil. 21 (5), 602–617.
Pessoa, L., 2008. On the relationship between emotion and cognition. Nat. Rev. Neurosci. 9 (2), 148.
Posner, M.I., Cohen, Y., 1984. Components of visual orienting. In: Bouma, H., Bouwhuis, D. (Eds.), Attention and Performance X, pp. 531–556.
Ro, T., Farnè, A., Chang, E., 2003. Inhibition of return and the human frontal eye fields. Exp. Brain Res. 150 (3), 290–296.
Schneider, W., Eschman, A., Zuccolotto, A., 2002. E-prime Reference Guide. Psychology Software Tools, Inc, Pittsburgh.
Sapir, A., Hayes, A., Henik, A., Danziger, S., Rafal, R., 2004. Parietal lobe lesions disrupt saccadic remapping of inhibitory location tagging. J. Cogn. Neurosci. 16 (4), 503–509.
Sapir, A., Soroker, N., Berger, A., Henik, A., 1999. Inhibition of return in spatial attention: direct evidence for collicular generation. Nat. Neurosci. 2 (12), 1053.
Tottenham, N., Tanaka, J.W., Leon, A.C., McCarry, T., Nurse, M., Hare, T.A., et al., 2009. The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Res. 168 (3), 242–249.
Van Koningsbruggen, M.G., Gabay, S., Sapir, A., Henik, A., Rafal, R.D., 2009. Hemispheric ansymmetry in the remapping and maintenance of visual salience maps: a TMS study. J. Cogn. Neurosci. 22 (8), 1730–1738.
Vivas, A.B., Fuentes, L.J., 2001. Stroop interference is affected in inhibition of return. Psychon. Bull. Rev. 8 (2), 315–323.
Vivas, A.B., Fuentes, L.J., Estevez, A.F., Humphreys, G.W., 2007. Inhibitory tagging in inhibition of return: evidence from flanker interference with multiple distractor features. Psychon. Bull. Rev. 14 (2), 320–326.
Vivas, A.B., Humphreys, G.W., Fuentes, L.J., 2003. Inhibitory processing following damage to the parietal lobe. Neuropsychologia 41, 1531–1540.
Vivas, A.B., Humphreys, G.W., Fuentes, L.J., 2006. Abnormal inhibition of return: a review and new data on patients with parietal lobe damage. Cogn. Neuropsychol. 23 (7), 1049–1064.
Vivas, A.B., Paraskevopoulos, E., Castillo, A., Fuentes, L.J., 2019. Neurophysiological activations of predictive and non-predictive exogenous cues: a cue-elicited EEG study on the generation of inhibition of return. Front. Psychol.: Cognition 10, 1–10, 227.
Weinberger, D.R., 1988. Schizophrenia and the frontal lobe. Trends Neurosci 11 (8), 367–370.
Yavari, F., Jamil, A., Samani, M.M., Vidor, L.P., Nitsche, M.A., 2018. Basic and functional effects of transcranial Electrical Stimulation (tES)—an introduction. Neurosci. Biobehav. Rev. 85, 81–92.
Zhang, Y., Zhou, X., Zhang, M., 2012. Temporary inhibitory tagging at previously attended locations: evidence from event-relate potentials. Psychophysiology 49 (9), 1191–1199.
Zhao, X., Li, X., Shi, W., 2017. Influence of inhibitory tagging (IT) on emotional and cognitive conflict processing: evidence from event-related potentials. Neurosci. Lett. 657, 120–125.